Telavancin for the Treatment of Nosocomial Pneumonia

Theravance, Inc.

Anti-Infective Drugs Advisory Committee

November 29, 2012

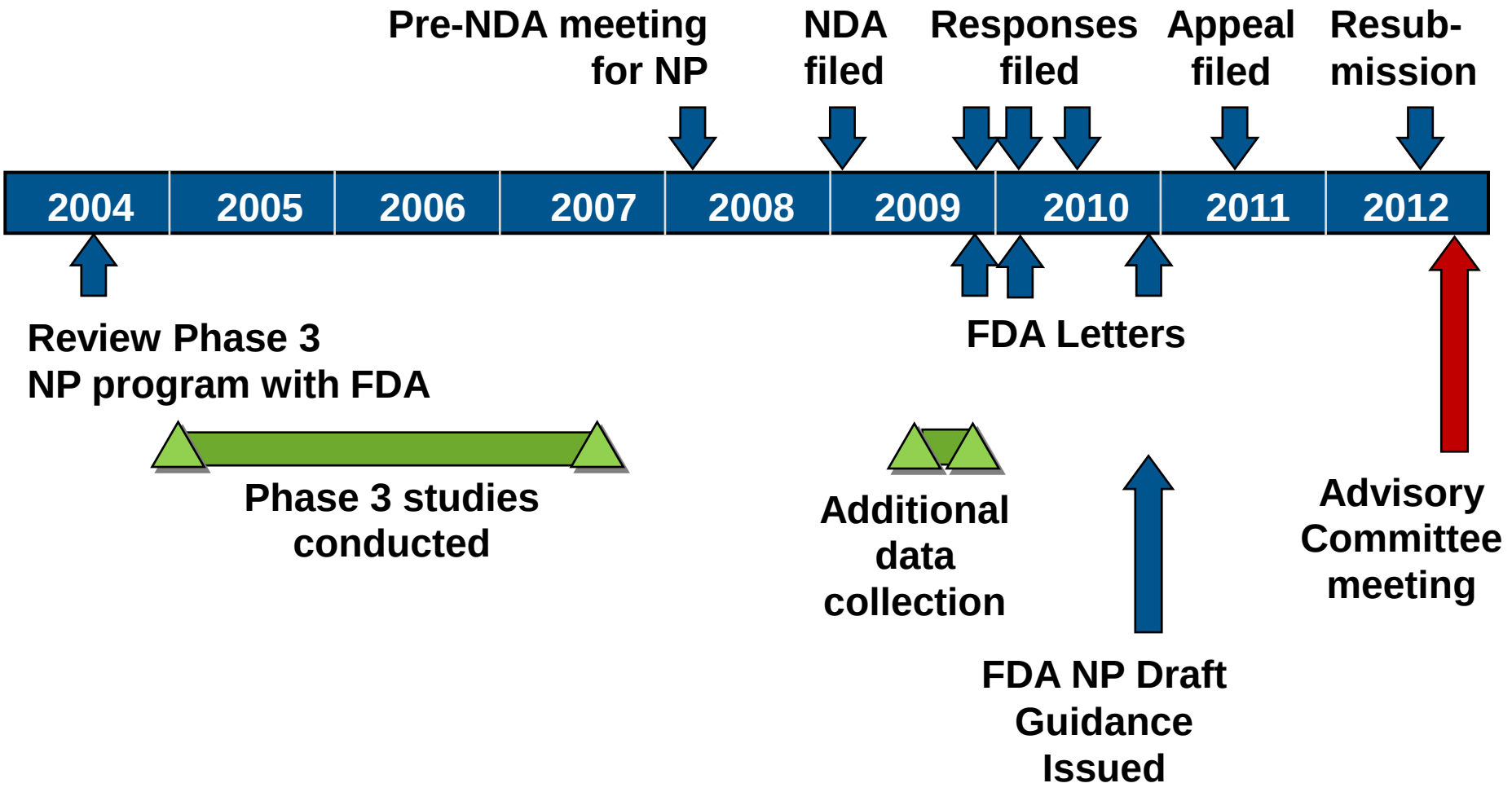
Agenda

Introduction	**Rebecca Coleman, PharmD** ***VP, Regulatory Affairs & Quality*** ***Theravance, Inc.***
Medical Need	**Marin Kollef, MD** ***Professor of Medicine, Pulmonary and Critical Care*** ***Washington University, St. Louis***
Efficacy	**Steven Barriere, PharmD** ***VP, Clinical & Medical Affairs*** ***Theravance, Inc.***
Safety	**Mathai Mammen, MD, PhD** ***SVP, Research and Early Clinical Development*** ***Theravance, Inc.***
Benefit Risk	**Louis Saravolatz, MD** ***Professor of Medicine, Infectious Diseases*** ***St. John Hospital, Detroit***
Conclusion	**Steven Barriere, PharmD** ***Theravance, Inc.***

VIBATIV® (telavancin) for Injection Approvals

- Approved in US and Canada for treatment of cSSSI due to susceptible Gram-positive pathogens
- Approved for NP due to MRSA in EU
- Marketed use ~ 125,000 patients

Development and Regulatory History in NP



Proposed Indication

VIBATIV (telavancin) is indicated for

- **Treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP), caused by susceptible isolates of the following Gram-positive microorganisms:**
  - ***Staphylococcus aureus*** **(including methicillin-susceptible and -resistant isolates) or**
  - ***Streptococcus pneumoniae***

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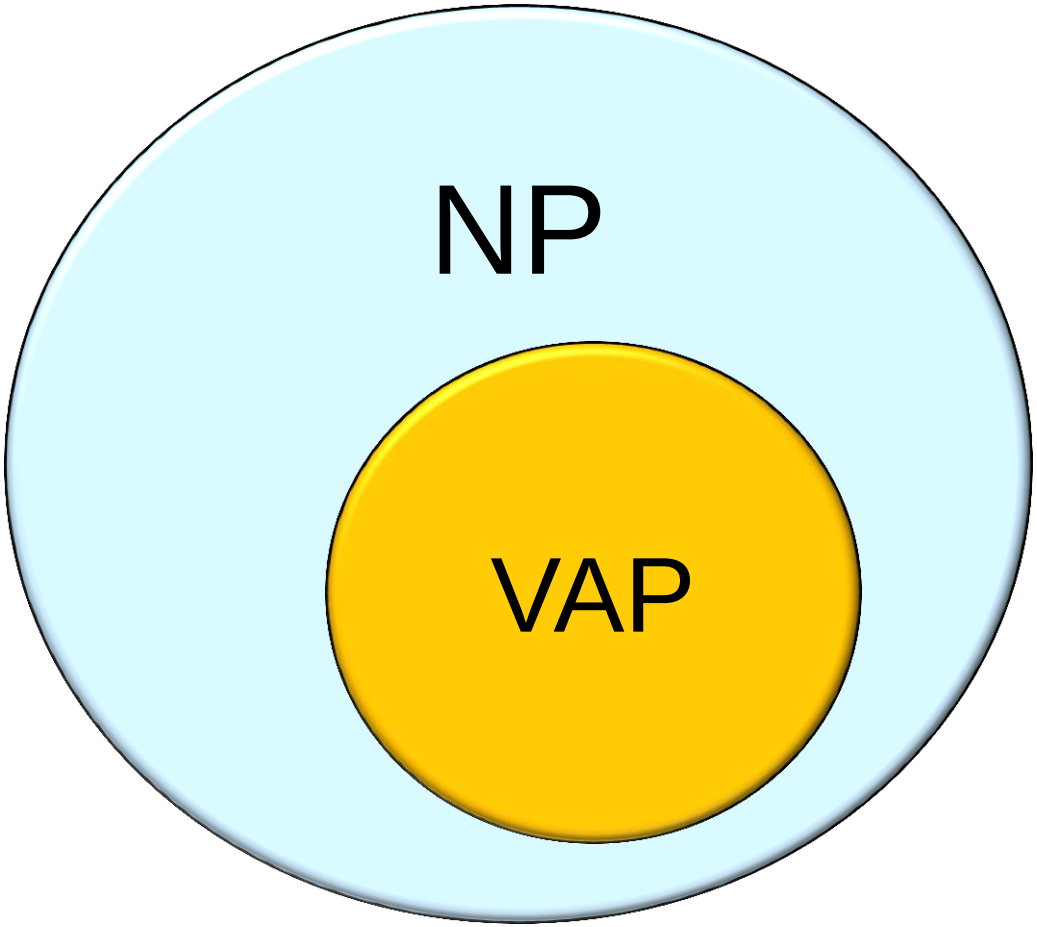
Medical Need in Nosocomial Pneumonia due to Gram-positive Pathogens

Marin Kollef, MD

Washington University, St. Louis

Nosocomial Pneumonia

- **Nosocomial pneumonia (NP) occurs ≥ 48 hr after admission and does not appear to be incubating at time of admission**
- **Ventilator-associated pneumonia (VAP) is a subtype of NP that develops > 48 - 72 hr after endotracheal intubation**



Criteria for Initiating Empiric Antibiotics

- **ATS/IDSA 2005 criteria for initiation of empiric antibiotic therapy for NP**
  - **Presence of a new or progressive infiltrate**
  - **Plus at least 2 of 3 clinical features**
    - **Fever > 38°C**
    - **Leukocytosis or leukopenia**
    - **Purulent secretions**

ATS/IDSA = American Thoracic Society / Infectious Disease Society of America

***AJRCCM*. ATS/IDSA 2005;V171,388-416.**

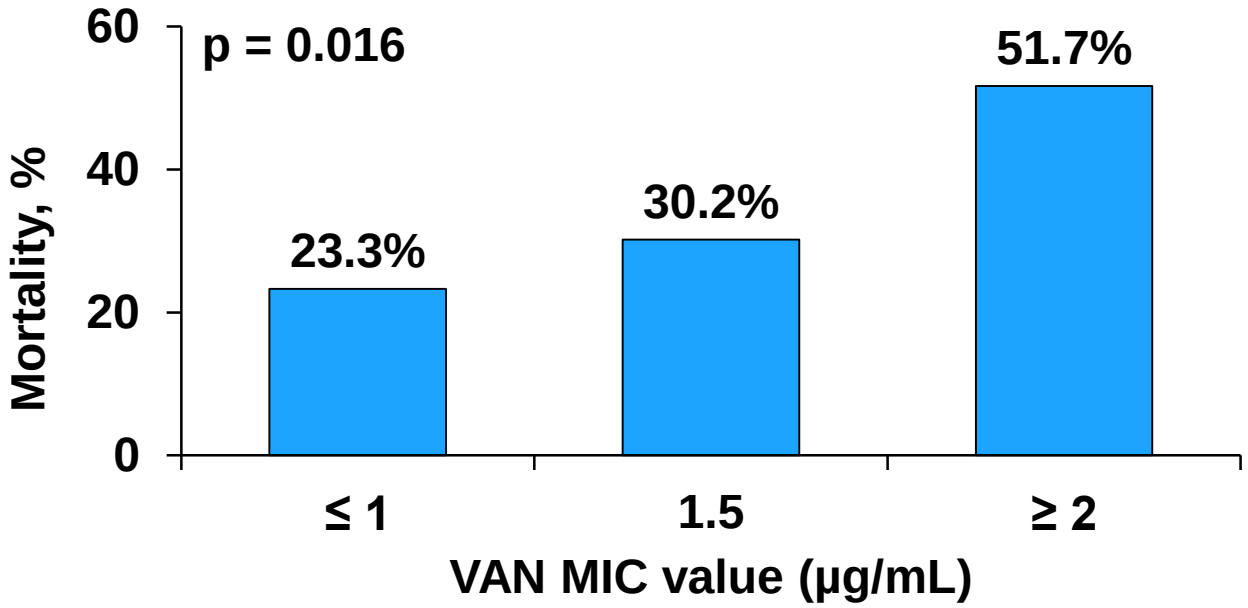
Impact of Nosocomial Pneumonia

- 2nd most common nosocomial infection in US
  - 5 to 10 cases per 1000 admissions
  - Up to 27% of all ICU infections
  - VAP in 9 - 27% of intubated patients
- Associated with highest rate of mortality among hospital-acquired infections
  - All-cause mortality 20 - 50%
  - Majority die from underlying conditions
  - Attributable mortality in VAP estimated at 5 -10%
- Increases hospital stay and costs of care

Richards, et al. *CCM*. 1999;27(5):887-92.
ATS/IDSA 2005, *AJRCCM*. v171:388-416.
CDC Respir Care. 1994;39:1191-1192.
Bekaert M, et al. *AJRCCM*. 2011;184:1133-39.
Fagon JY, et al. *Am J Med*. 1993;94:281-288.
Craven DE, et al. *Am Rev Respir Dis*. 1986;133:792-796.
Flanders, et al. *Am J of Infec Ctrl*, 2006;34(2):84-93.
Nguile-Makao M, et al. *ICM*. 2010;36:781-789.

In NP due to MRSA, Higher Vancomycin MICs Associated with Increased Mortality

- 158 ICU patients with NP due to MRSA from 4 US academic centers in 2006 to 2007



- Use vancomycin (VAN) with caution when MICs are between 1 and 2 and consider alternatives

MIC = minimum inhibitory concentration

Haque et al. *Chest*. 2010;138:1356-62.

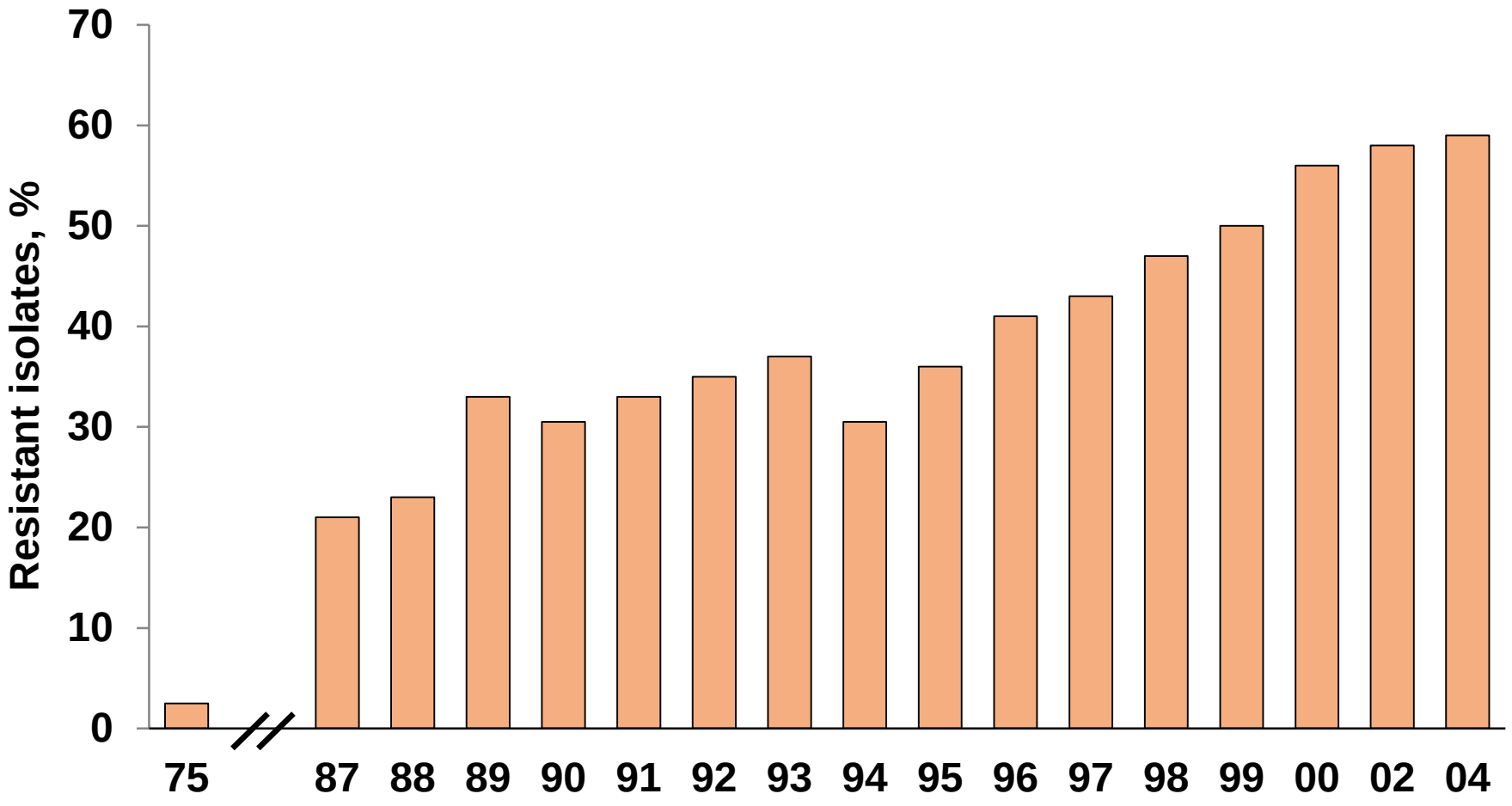
Etiology of Nosocomial Pneumonia

SENTRY program pathogens isolated from NP patients (2004-08); 31,436 cases

	Percent			
Pathogen (no.)	All Regions	US	Europe	Latin America
S. aureus	28.0	36.3	23.0	20.1
P. aeruginosa	21.8	19.7	20.8	28.2
Klebsiella spp.	9.8	8.5	10.1	12.1
E. coli	6.9	4.6	10.1	5.5
Acinetobacter spp.	6.8	4.8	5.6	13.3

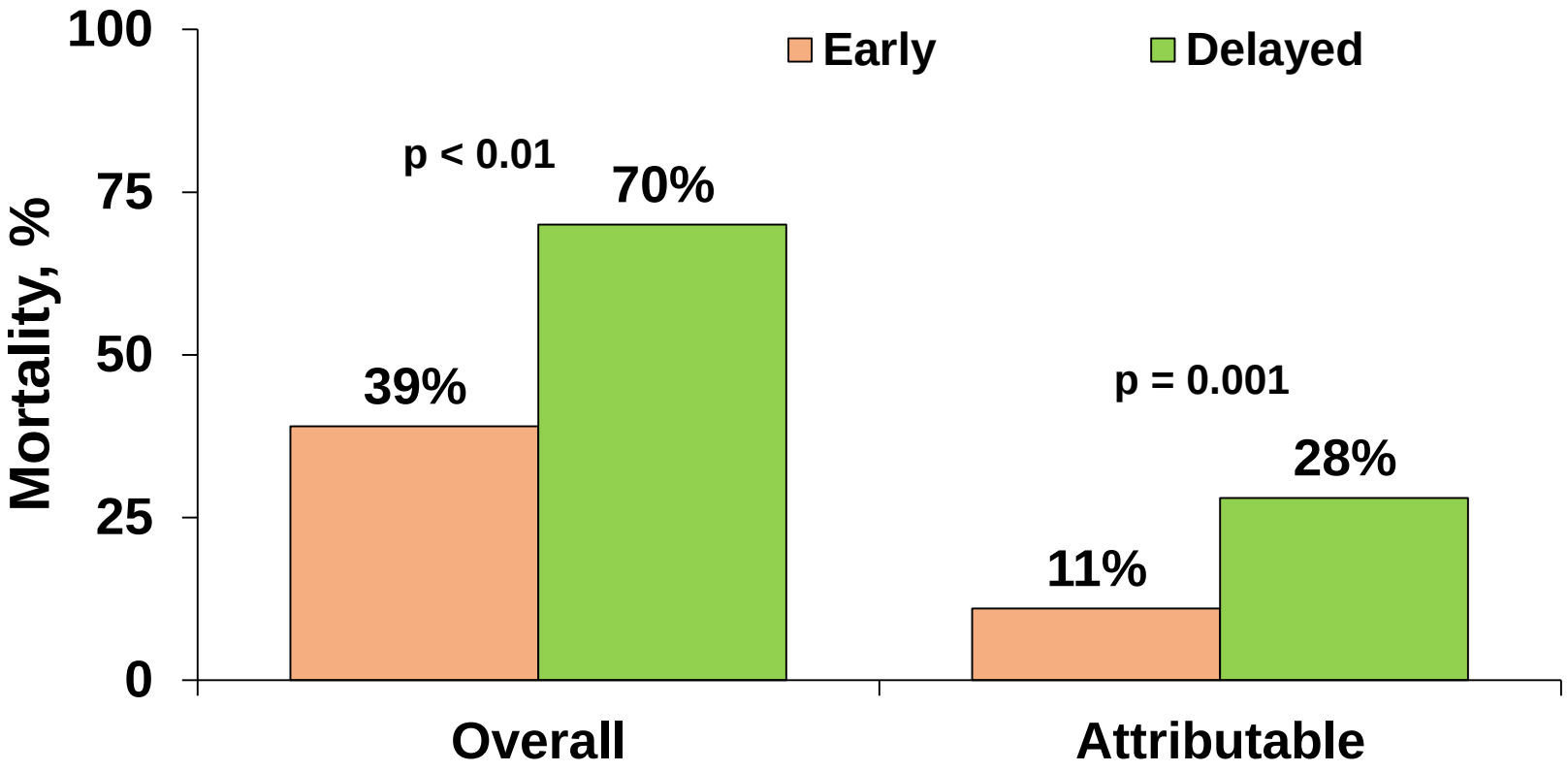
Jones et al. *CID*. 2010;51 (Suppl 1):S81-7.

Since 2000 Most *S. aureus* in US Hospitals have been MRSA



NNIS Antimicrobial Resistance Surveillance Report 2004
http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NNIS_2004.pdf

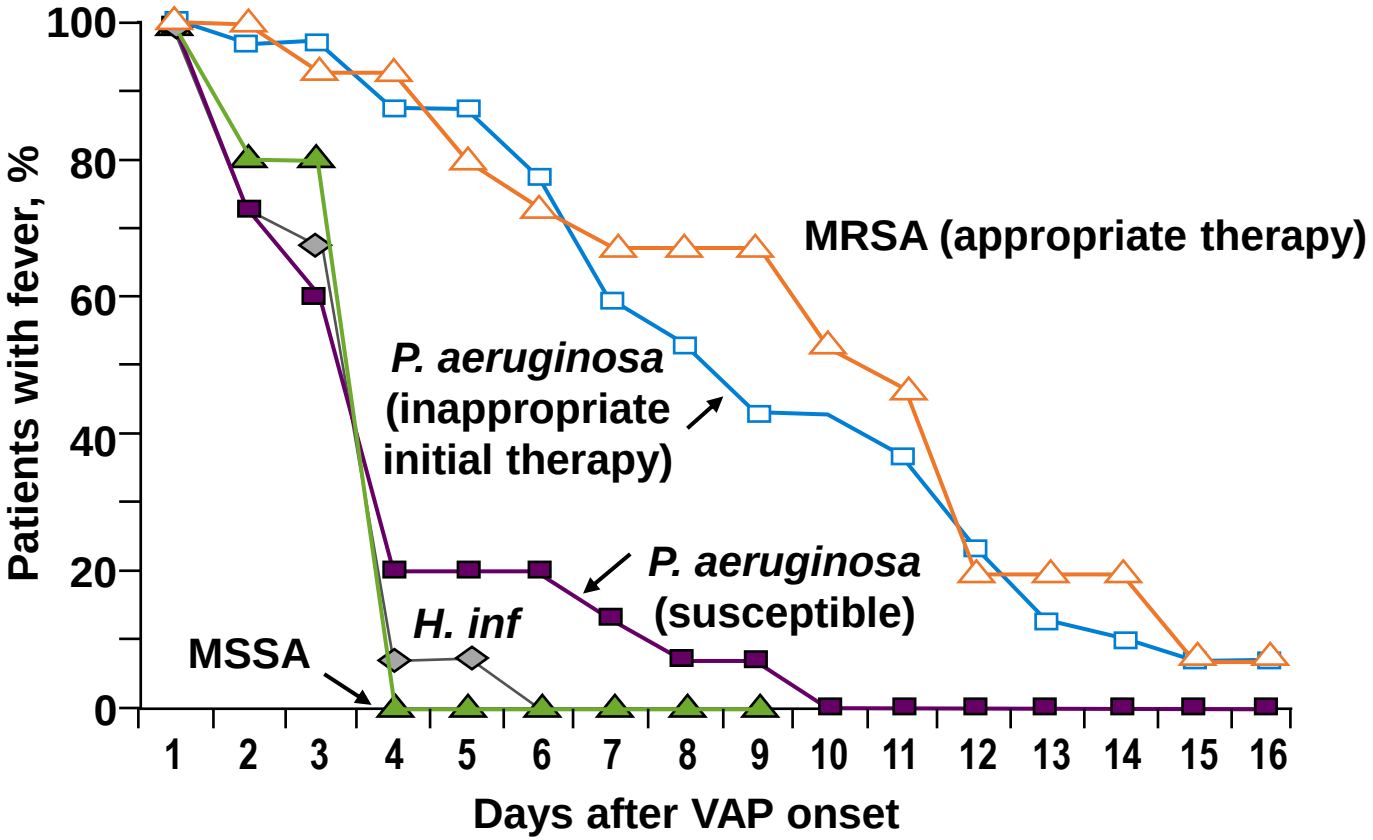
Early Appropriate Therapy is Critical in NP



- 107 patients with VAP. Mean time from diagnosis of VAP to initiation of appropriate therapy was 28.6 hr in delayed group vs. 12.5 hr in early group

Iregui M, et al. *Chest*. 2002;122:262-268.

Clinical Resolution of VAP Differs by Pathogen



- MRSA patients also required significantly longer respiratory support even when treated adequately

Vidaur L. *Chest.* 2008; 133:625-33.

Guidelines for Antibiotic Selection in NP when MRSA is of Concern

- **ATS/IDSA NP Guidelines**
  - **For empiric therapy in patients at risk for MDR pathogens:**
    - **Combination therapy that includes linezolid or vancomycin to cover MRSA**
- **IDSA MRSA Guidelines**
  - **For HA-MRSA or CA-MRSA pneumonia**
    - **Vancomycin or linezolid**
    - **Or clindamycin if the strain is susceptible**

ATS/IDSA 2005, *AJRCCM*. 171:388-416
Liu et al. *CID*. 2011;52:1-38.

Limitations of Approved NP Drugs for MRSA

- **Vancomycin**
  - **Uncertainty of dose**
  - **Nephrotoxicity with increasing dose**
  - **Infusion-associated reactions**
  - **Decreasing susceptibility**
- **Linezolid**
  - **Bacteriostatic**
  - **Warning: Should not be used in catheter-related infections (mortality imbalance in open-label study)**
  - **Drug interactions (monoamine oxidase inhibitors, adrenergic and serotonergic agents)**
  - **Metabolic/hematologic toxicities**
  - **Emerging resistance**

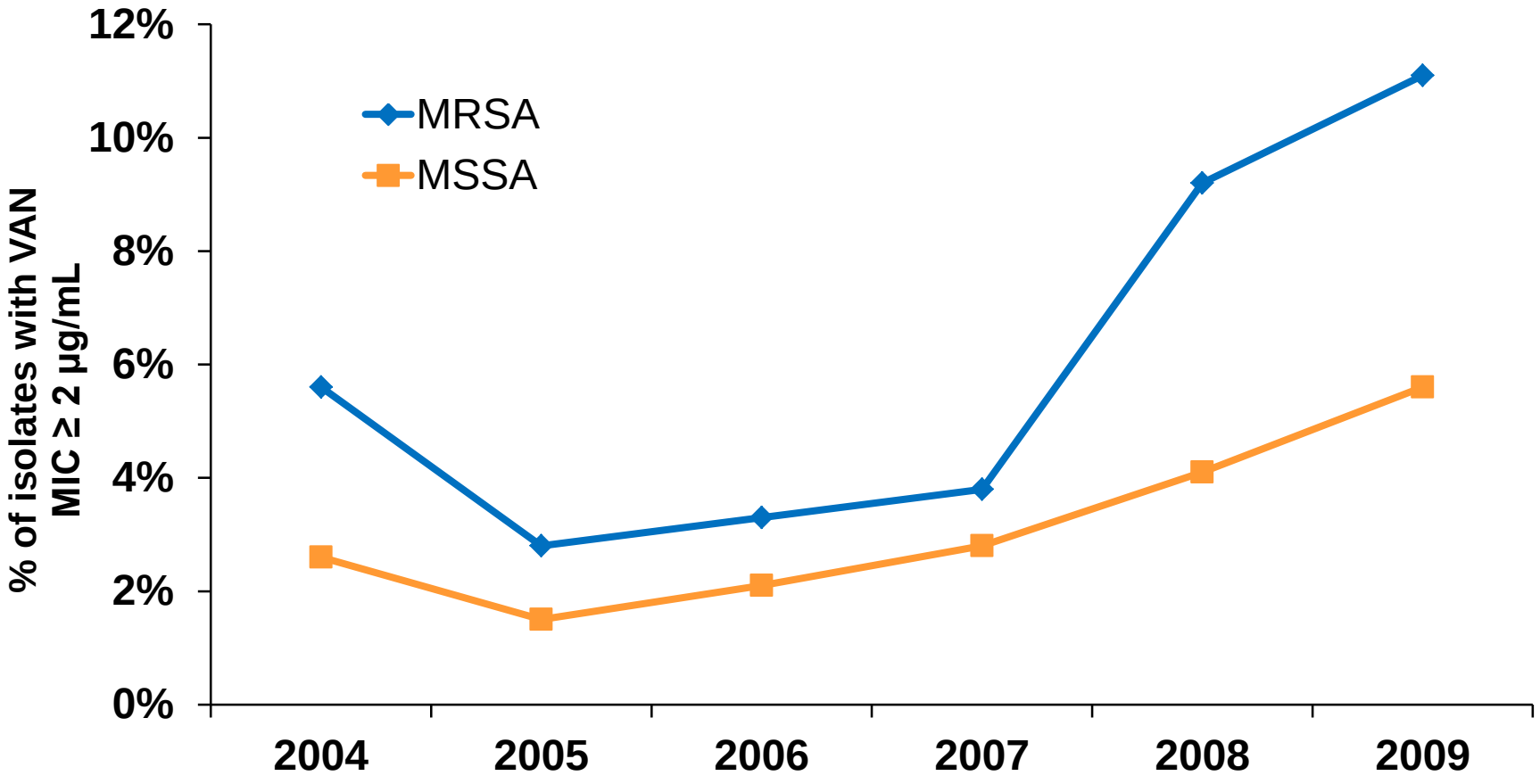
Vancomycin is Losing Effectiveness

- True vancomycin resistance (VRSA)
  - Rare
- hVISA: Subpopulations with high MICs
  - Worldwide estimate: 5 - 15% of MRSA are hVISA
  - Clinical failures with sustained hVISA bacteremia
  - Lack of diagnostic tools for rapid detection
- MIC creep in *S. aureus*
  - MICs 1.5 - 2 µg/mL predicts poor response to VAN
  - 11% of clinical isolates with MIC ≥ 2 in 2009
  - Prior vancomycin use predicts higher MICs

Rong, et al. *Ann Pharmacother*. 2010;44:844-850.
Hawser, et al. *IJAA*. 2011;37:219-24.
Choi, et al. *ICM*. 2011;37:639-47.
Moise, et al. *JAC*. 2008;61:85–90.
Lodise, et al. *JAC*. 2008;62:1138-41.
Van Hal, et al. *CID.* 2012;54:755-71.

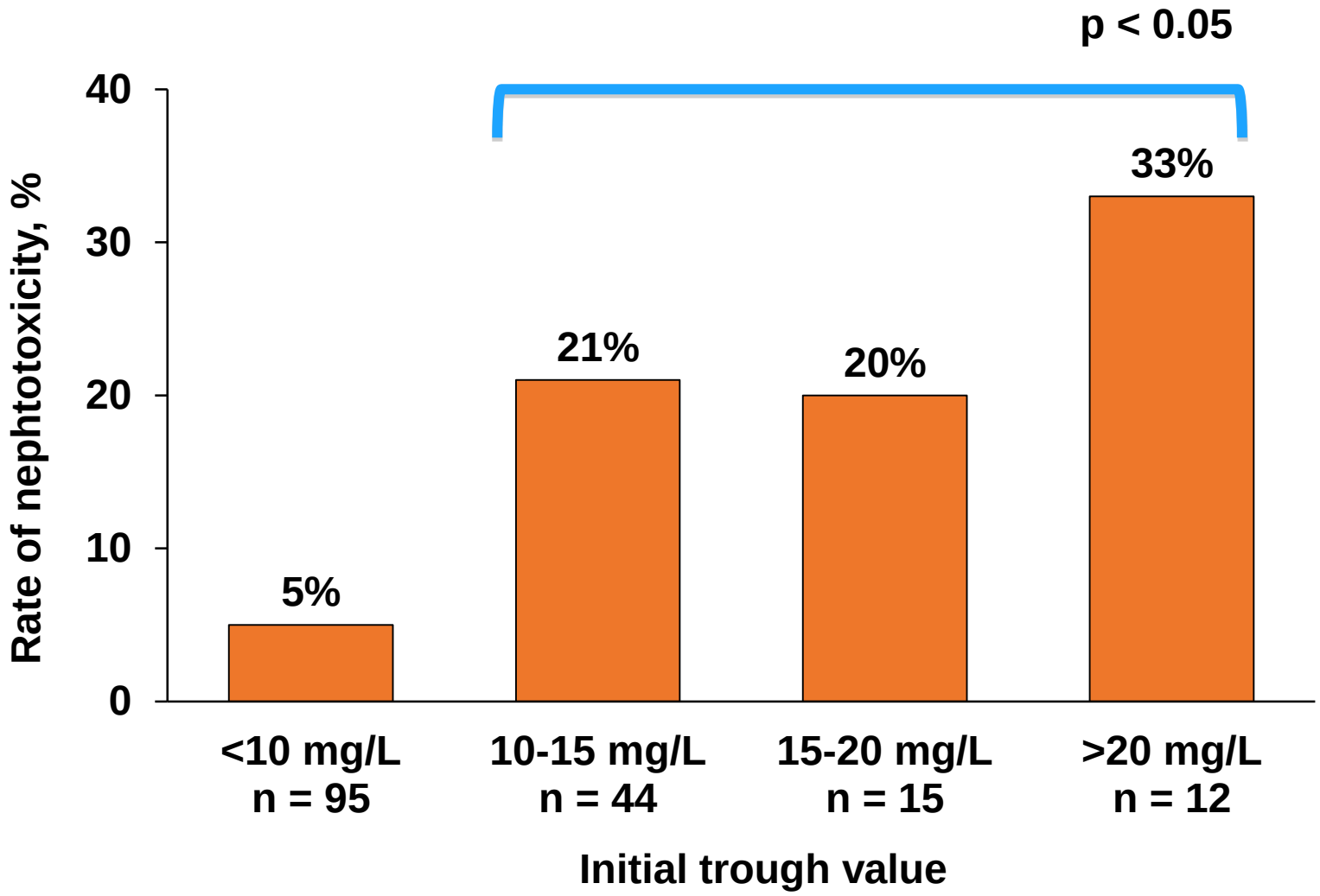
Increasing Proportion of MRSA with VAN MIC ≥ 2 µg/mL from 2004 to 2009

8249 MRSA & 11,755 MSSA clinical isolates from the tigecycline surveillance program



Hawser, et al. *IJAA*. 2011;37:219-24.

Increasing VAN Dose to Treat High MICs Increases Risk of Nephrotoxicity



Lodise TP, et al. *CID*. 2009;49: 507-14.

Linezolid Has Limitations

- Associated with
  - Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia)
  - Drug-drug interactions (serotonin syndrome)
  - Peripheral and optic neuropathy
- New resistance mechanism via cfr gene on transmissible plasmid
  - Cross resistance to 5 other antibiotic classes with little fitness cost
  - First outbreak: Madrid ICU in 2008
  - Now a global problem: Multi-city outbreak in Ohio

LaMarre, et al. *AAC*. 2011;55:3714-19
Bonilla, et al. *CID*. 2010;51:796-800

Conclusion: Increasing Challenge of Treating Nosocomial Pneumonia

- Significant impact on morbidity, mortality and cost of care
- MRSA the most common Gram-positive pathogen
  - Outcomes worse even with effective therapy
- Early appropriate therapy critical but only two approved therapies for NP due to MRSA
  - Both vancomycin and linezolid have limitations
  - Most importantly increasing rates of resistance

We Urgently Need Additional Effective Antibiotics for Patients with NP due to MRSA

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Efficacy

Steven Barriere, PharmD

VP, Clinical & Medical Affairs
Theravance, Inc.

Outline

- Overview of Telavancin
- Overview of NP Studies
- Analysis Considerations
- Randomization Results and Baseline Characteristics
- Pre-specified Clinical Response Endpoint
- Post Hoc 28-Day All-Cause Mortality Endpoint
- Conclusions

Telavancin Profile

- Dual mechanism of action, bactericidal effects
  - Inhibits cell wall synthesis
  - Disrupts bacterial membrane function
- Broad, potent Gram(+) spectrum
  - MSSA, MRSA MIC_{90}: 0.25 µg/mL
  - Comparable potency vs hVISA/VISA, linezolid-resistant strains
- Low potential for emergence of resistance
- Efficacy demonstrated in multiple animal models
  - Pneumonia, endocarditis, sepsis
- Linear, predictable PK
  - Effective lung concentrations
- No decrease in antibacterial activity with renal impairment

Worldwide Update (2010) of TLV Activity Against Gram(+) NP Pathogens

		MIC (µg/mL)		
		Range	50%	90%
MSSA, N = 4565	Telavancin	0.03 - 0.5	0.12	0.25
	Vancomycin	0.25 - 2	1	1
	Daptomycin	≤ 0.06 - 1	0.25	0.5
	Linezolid	≤ 0.12 - 2	1	2
MRSA, N = 3088	Telavancin	≤ 0.015 - 0.5	0.12	0.25
	Vancomycin	0.25 - 2	1	1
	Daptomycin	≤ 0.06 - 2	0.25	0.5
	Linezolid	≤ 0.12 - 8	1	1
S. pneumoniae, N = 2150	Telavancin	≤ 0.015 - 0.12	≤ 0.015	0.03
	Vancomycin	≤ 0.12 - 1	0.25	0.5
	Linezolid	≤ 0.12 - 4	1	1
	Penicillin	≤ 0.03 - > 4	≤ 0.03	4

Mendes RE, et al. *AAC*. 2012;56:3999-04.

Comparative Activity of Telavancin Against 33 Strains of VISA*

	MIC range	MIC_{50}	MIC_{90}	% Non-susceptible
Telavancin	0.25 - 1	0.5	0.75	0
Linezolid	0.5 - 4	2	4	0
Ceftaroline	0.25 - 2	0.5	2	15
Daptomycin	1 - 8	2	4	70
Vancomycin	4 - 8	4	8	100

*** Vancomycin-intermediate *S. aureus;* clinical isolates from NARSA**
Saravolatz LD, et al. *CID.* 2012;55:582–6.

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ATTAIN Study Design Overview

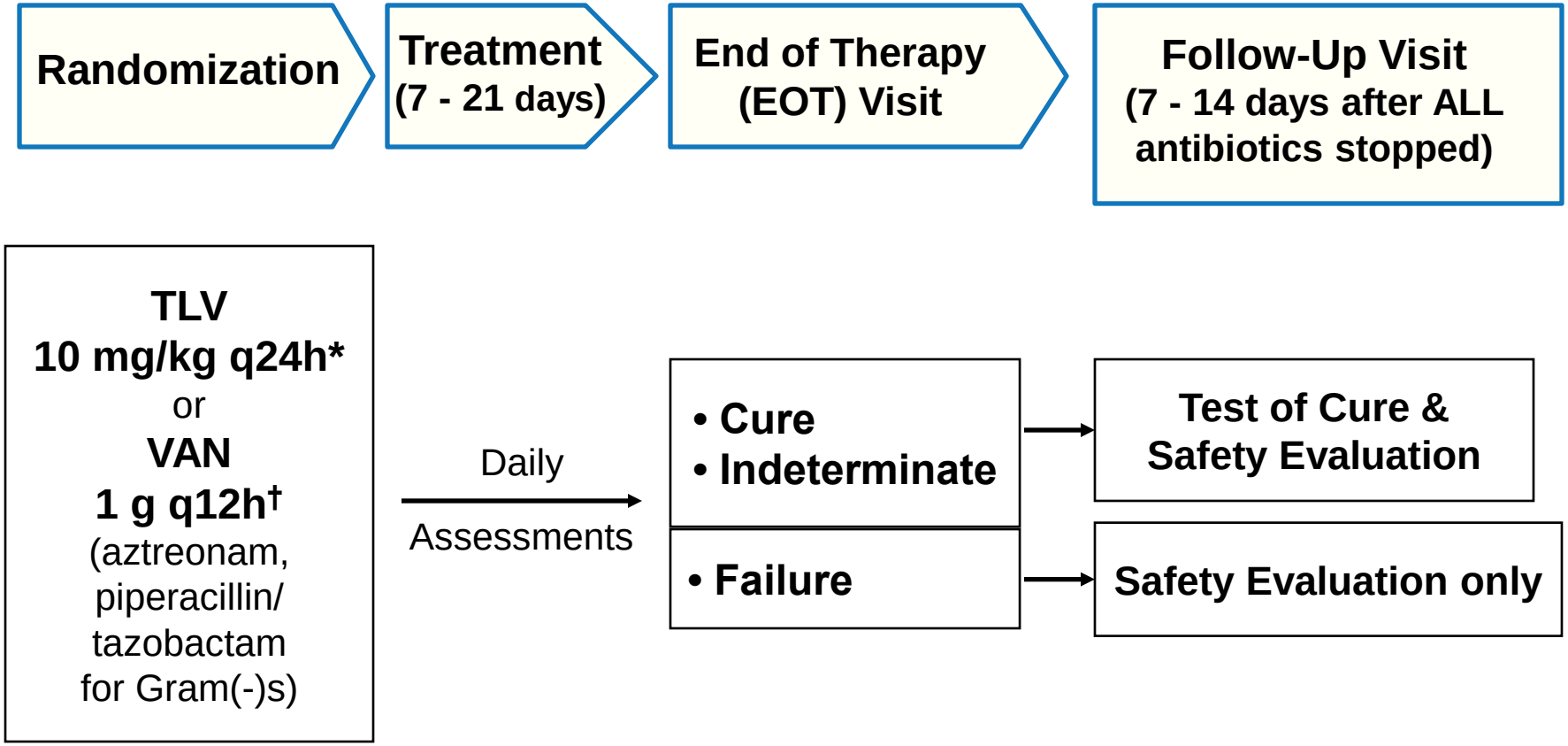
- **Two studies conducted under identical protocols**
  - **ATTAIN 1 (Study 0015)**
  - **ATTAIN 2 (Study 0019)**
  - **Each study was a randomized, double-blind, multicenter, multinational, Phase 3 trial to evaluate efficacy and safety of TLV vs. VAN in patients with NP, with focus on MRSA**
- **274 sites in 38 countries enrolled from January 2005 – June 2007**
  - **22% patients enrolled from US sites**

Rubinstein E, et al. *CID*. 2011;52:31-40.

Pre-Specified Study Objectives

- **Primary**
  - **Demonstrate noninferiority of TLV compared with VAN in clinical response at Test-of-Cure in the All-Treated and Clinically Evaluable populations**
- **Key secondary**
  - **Demonstrate superiority in clinical response of TLV vs. VAN in pooled population of patients from both studies who had MRSA as baseline pathogen**
- **Other secondary endpoints included mortality**
- **Clinical response was the investigator's assessment of resolution of clinical signs and symptoms of NP**
- **Safety assessments**
  - **Vital signs, AEs, ECGs, laboratory parameters**

Study Design



*** Dosage adjustment for renal insufficiency per protocol.**

† Dosage adjustment for weight and/or renal function per institutional policy.

Inclusion / Exclusion Criteria

- Identical for two studies
- Matched those for prior successful linezolid NP registrational trial*
- Designed to enroll patients with pneumonia
- Included patients likely to respond to study medications
  - Only VAN-susceptible strains
  - Limited use of prior antibiotic therapy
- Minimized potential confounding factors such as potentially effective non-study antibiotics
  - Limited choice of drugs for Gram(-) coverage

* Rubinstein E, et al. *CID*. 2001;32:402-1.2

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Outcome Evaluations at Test of Cure

- **Objective criteria (body temp, WBC, oxygenation, etc) used to assess clinical response**
- **Cure**
  - **Signs and symptoms resolved, no antibiotic therapy for NP after EOT, and baseline radiographic findings improved or did not progress**
- **Failure**
  - **Failure at EOT**
  - **Relapsed pneumonia after EOT due to same Gram(+) pathogen**
  - **Death on or after Day 3 attributable to NP**
- **Indeterminate**
  - **Inability to determine outcome**

Pre-Specified Analysis Populations

Population	Definition
All-Treated (AT)*	All patients who received any amount of study medication
Modified All-Treated (MAT)	All patients in AT population with baseline respiratory pathogen identified from respiratory tract or blood cultures
Clinically Evaluable (CE)*	All patients in AT population (1) with adherence to protocol, or (2) who died on or after Study Day 3, where death is attributable to the NP episode under study
Microbiologically Evaluable (ME)	All patients in CE population who also had Gram(+) pathogen recovered from respiratory specimens or blood cultures

* Co-primary analysis population for efficacy

Rationale for Pooling

- Pooling of studies for evaluation of efficacy vs. MRSA was prespecified
- Using an identical protocol, studies represent random samples from the same population
  - NP population is complex; patients with multiple comorbid conditions
  - Differences observed in baseline characteristics between studies are random
  - Pooled data are more representative of true NP population
- Pooling results in sufficient statistical power for subgroup analysis

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Randomization Results and Disposition

	TLV	VAN
Randomized, N	767	765
Randomized but not treated, n	18	11
Received study medication*, n	749	754

	Patients, n (% of AT) N = 1503	
All-treated (AT)	749 (100)	754 (100)
Modified all-treated (MAT)	560 (75)	529 (70)
Clinically evaluable (CE)	312 (42)	342 (45)
Microbiologically evaluable (ME)	243 (32)	237 (31)

* Two patients randomized to vancomycin received telavancin

Baseline Characteristics
AT Population

	Patients, n (%)			
	0015		0019	
	TLV N = 372	VAN N = 374	TLV N = 377	VAN N = 380
Male, %	63	57	67	67
Age, mean ± SD, yr	63 ± 19.2	64 ± 17.3	61 ± 17.8	62 ± 18.0
Age ≥ 75 yr	131 (35)	124 (33)	99 (26)	109 (29)
ICU at baseline	224 (60)	216 (58)	207 (55)	224 (59)
Diabetes	118 (32)	114 (30)	85 (23)	77 (20)
CHF	71 (19)	78 (21)	59 (16)	63 (17)
COPD	86 (23)	90 (24)	87 (23)	88 (23)
Chronic kidney disease	32 (9)	35 (9)	11 (3)	17 (4)
Acute renal failure	43 (12)	35 (9)	30 (8)	29 (8)
CrCL ≤ 50 mL/min	146 (39)	145 (39)	109 (29)	105 (28)
APACHE II Score, mean ± SD	16 ± 6.6	16 ± 6.3	15 ± 6.2	16 ± 6.6

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease;
APACHE = Acute Physiology and Chronic Health Evaluation

Baseline NP Characteristics
AT Population

	Patients, n (%)			
	0015		0019	
	TLV N = 372	VAN N = 374	TLV N = 377	VAN N = 380
VAP	103 (28)	100 (27)	113 (30)	111 (29)
Late VAP*	91 (88)	81 (81)	98 (87)	90 (81)
ARDS/ALI	57 (15)	40 (10)	27 (7)	23 (6)
Multilobar pneumonia	238 (64)	229 (61)	235 (62)	231 (61)
Prior treatment failure	88 (24)	86 (23)	127 (34)	125 (33)
Shock	14 (4)	23 (6)	15 (4)	18 (5)

* ≥ 4 days post-intubation, denominator is patients with VAP

Baseline Gram(+) Pathogens from Respiratory Cultures – MAT Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV	VAN
Gram(+) pathogens	401 (100)	383 (100)
S. aureus	367 (92)	348 (91)
MRSA	228 (57)	230 (60)
hVISA	22 (10)	16 (7)
MSSA	144 (36)	120 (31)
S. pneumoniae	29 (7)	30 (8)
Gram(+) only	257 (64)	258 (67)
Mixed (Gram (+),(-) pathogens)	144 (36)	125 (33)

Prior and Concomitant Antibiotic Therapy

Selected prior antibiotic therapy (≤ 24 hr)
Patients, n (%)

	TLV N = 749	VAN N = 754
Vancomycin	142 (19)	147 (20)
Linezolid	3 (< 1)	7 (< 1)
TMP-SMX	2 (< 1)	0

- Majority of patients received Gram(-) coverage during study
  - 59% aztreonam
  - 22% piperacillin / tazobactam
  - 10% imipenem
- Inadequate Gram(-) coverage defined as no antibiotics active against baseline pathogen or delayed until ≥ Day 3

TMP-SMX = Trimethoprim-sulfamethoxazole

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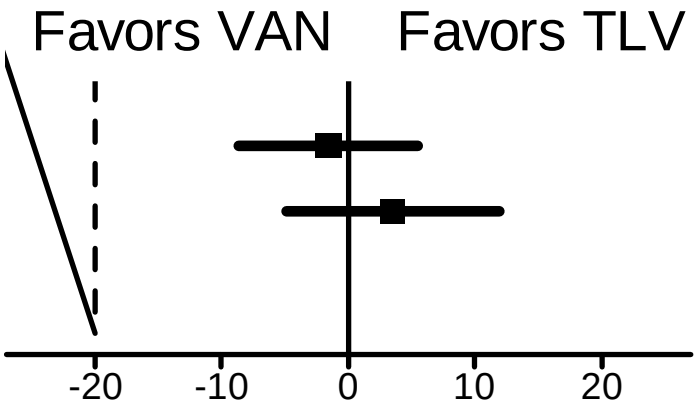
Primary Endpoint: Clinical Response (Cure Rates) at Test-of-Cure

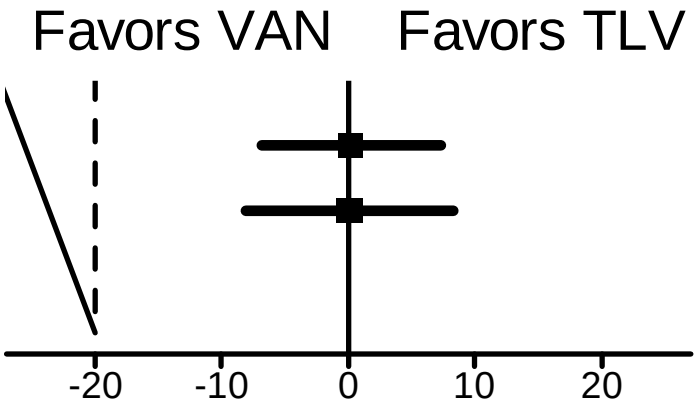
Study 0015

	N	TLV %	VAN %	Delta*	95% CI
AT	746	57.5	59.1	-1.6	(-8.6, 5.5)
CE	313	83.7	80.2	3.5	(-5.1, 12)



Study 0019

	N	TLV %	VAN %	Delta*	95% CI
AT	757	60.2	60.0	0.2	(-6.8, 7.2)
CE	341	81.3	81.2	0.1	(-8.2, 8.4)



* Delta = Difference in cure rates (TLV - VAN)

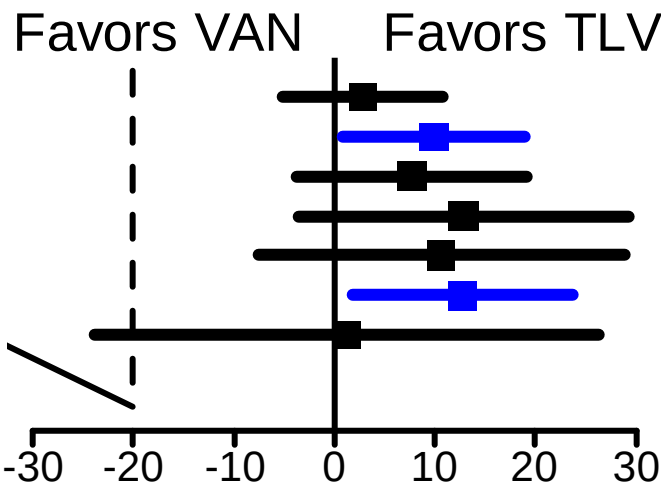
Patients Who Died Following Cure

- 33 patients cured who subsequently died by Day 28
  - 17 telavancin patients and 16 vancomycin patients
  - Represents 4% of all patients cured
  - 5 telavancin patients and 6 vancomycin patients died within 2 days of cure
- 96% of patients who were cured were alive at Day 28

Cure Rates by Gram(+) Baseline Pathogen
ME Population (Studies 0015, 0019)

Studies 0015,0019-ME

	N	Delta	95% CI
Any S.aureus	433	2.8	(-5.1, 10.8)
Mono S. aureus	298	9.9	(0.8, 19)
Mono MRSA	204	7.7	(-3.7, 19)
Mono MSSA	94	12.9	(-3.5, 29.4)
VAN MIC<=0.5	65	10.6	(-7.9, 28.9)
VAN MIC>=1	190	12.8	(1.8, 23.8)
Mono S. pneumonaie	26	1.2	(-22.7, 26.3)



Mono = monomicrobial

Cure Rates in Subgroups of Clinical Interest
CE Population (Studies 0015, 0019)

	n	% Cure		Difference TLV – VAN (95% CI)
		TLV	VAN	
VAP*	135	80.0	66.2	13.8 (-1.0, 28.7)
Bacteremia*	29	86.7	78.6	8.1 (-20.5, 35.3)
Age ≥ 65 yr*	347	80.6	76.0	4.6 (-4.1, 13.3)
APACHE II ≥ 20*	117	69.6	59.0	10.6 (-6.6, 27.9)
hVISA†	15	71.4	37.5	33.9 (-16.6, 69.9)

* Prospectively defined subgroups
† Monomicrobial infection in the MAT population

Clinical Response Summary

- **TLV non-inferior to VAN in pre-specified analysis populations for primary endpoint**
- **Higher cure rates for TLV observed in patients with**
  - **Monomicrobial *S. aureus* infections (both MSSA and MRSA)**
  - ***S. aureus* with higher VAN MIC**
  - **Groups of clinical interest**
    - **Bacteremic, elderly, VAP, high APACHE II score**

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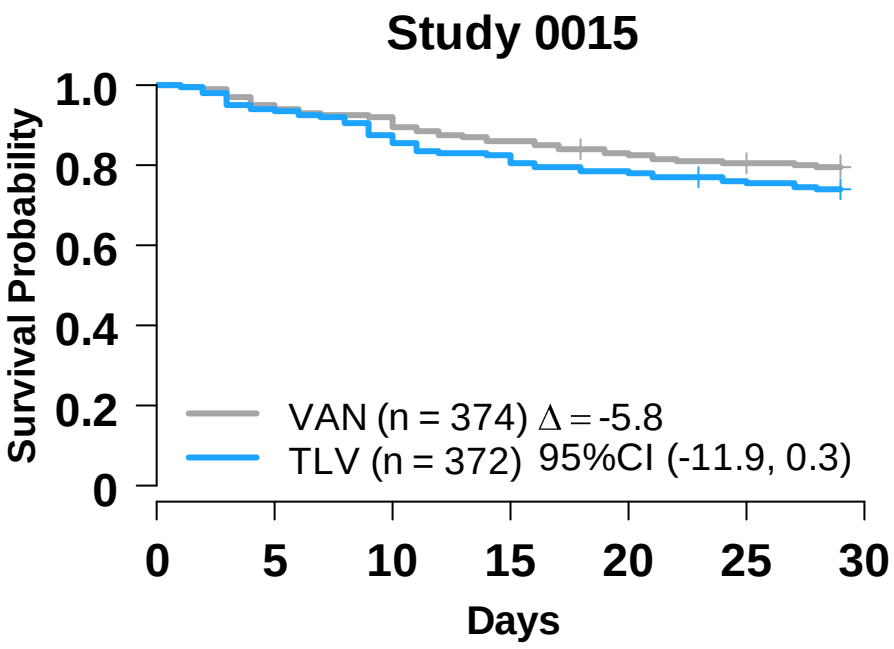
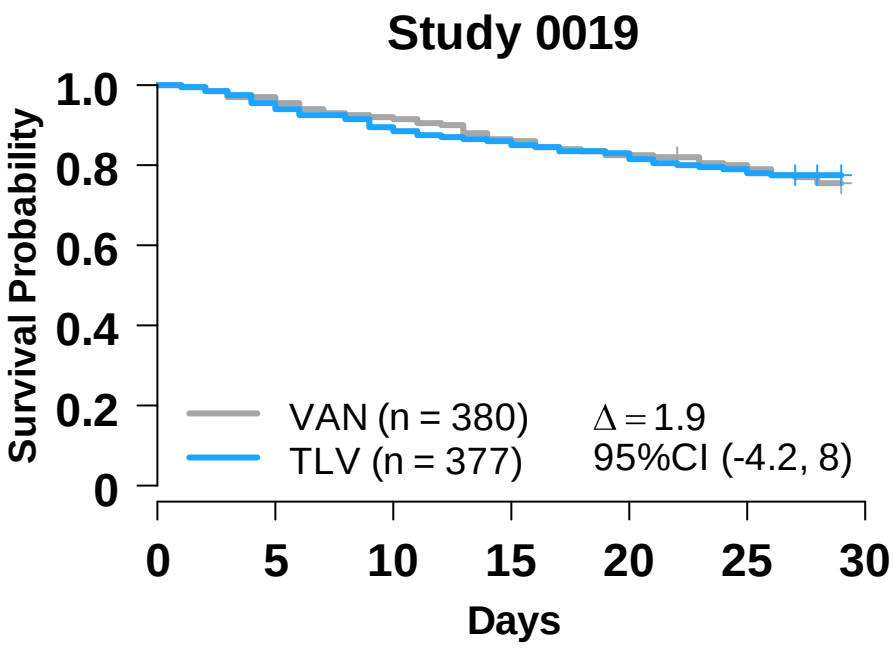
Post Hoc Analysis of 28-Day All-Cause Mortality

- Obtained survival status for 95% of patients at 28 days
- Draft HABP/VABP drug development guidelines
  - NI margin of 10% identified in studies in which the control mortality is ≥ 20%
- Primary endpoint: All-cause mortality at 28 days post-randomization
  - Mortality proportion is Kaplan Meier estimate at 28 days

KM Survival Curves by Study
AT Population





Higher mortality in TLV group in Study 0015, lower in Study 0019

All-Cause Mortality Analysis: ATS/IDSA Population

- American Thoracic Society / Infectious Diseases Society of America Guidelines (ATS/IDSA)
  - Guideline for the Management of Adults with HAP, VAP and HCAP
  - Optimal balance of sensitivity/specificity for identification of NP
- Inclusion criteria in November 2010 FDA Draft Guidance
- Baseline characteristics of ATS/IDSA–AT similar to overall AT population
  - Less chronic cardiopulmonary disease and more consistent with pneumonia

Key Post Hoc Mortality Analysis Groups

Analysis group (% of AT population)	Definition
ATS/IDSA–AT (86%)	Patients in the AT population meeting ATS/IDSA criteria
ATS/IDSA–PP (46%)	As above and at least 1 Gram(+) respiratory pathogen recovered from baseline cultures (includes mixed infections)
ATS/IDSA–MPP (30%)	As above but only Gram(+) respiratory pathogen(s) recovered from baseline cultures

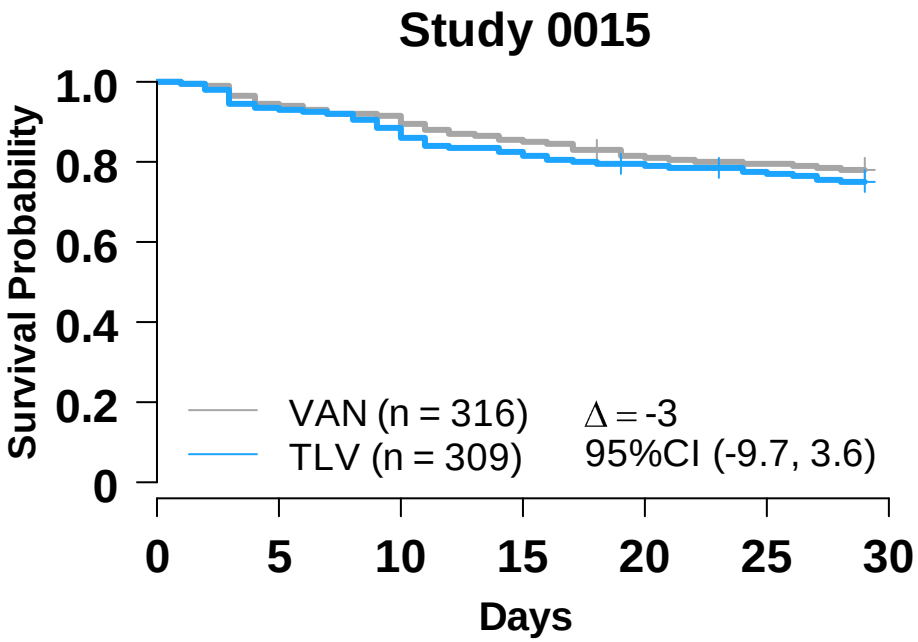
Post Hoc Mortality Power

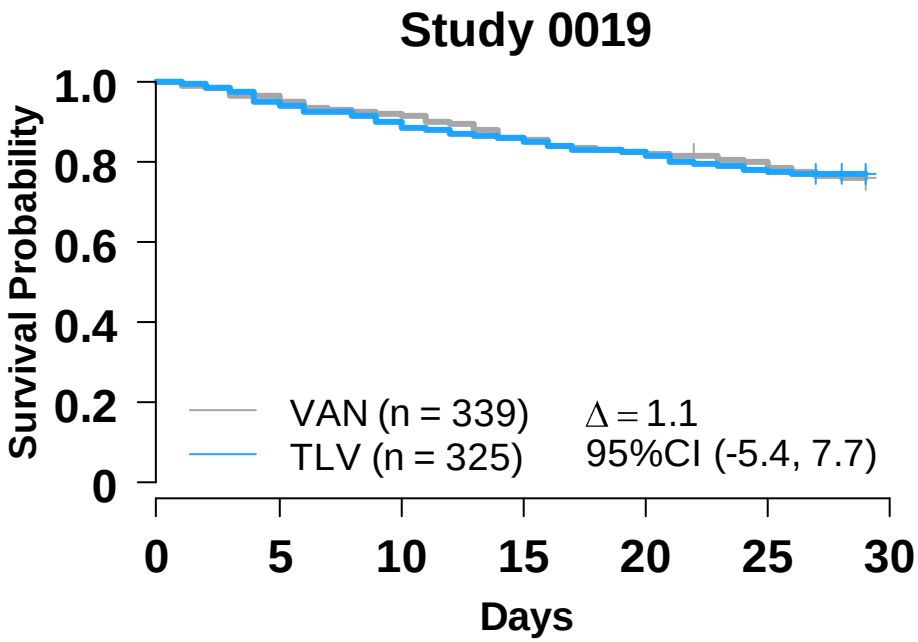
- **Power calculations for all-cause mortality endpoint**

	Post hoc power, %		
Analysis group	Study 0015	Study 0019	Studies 0015 & 0019
ATS/IDSA–AT	88	90	99
ATS/IDSA–PP	59	67	90
ATS/IDSA–MPP	47	45	75

- **Aggregated results presented to provide more representative and thus, more exhaustive sample of the NP population**

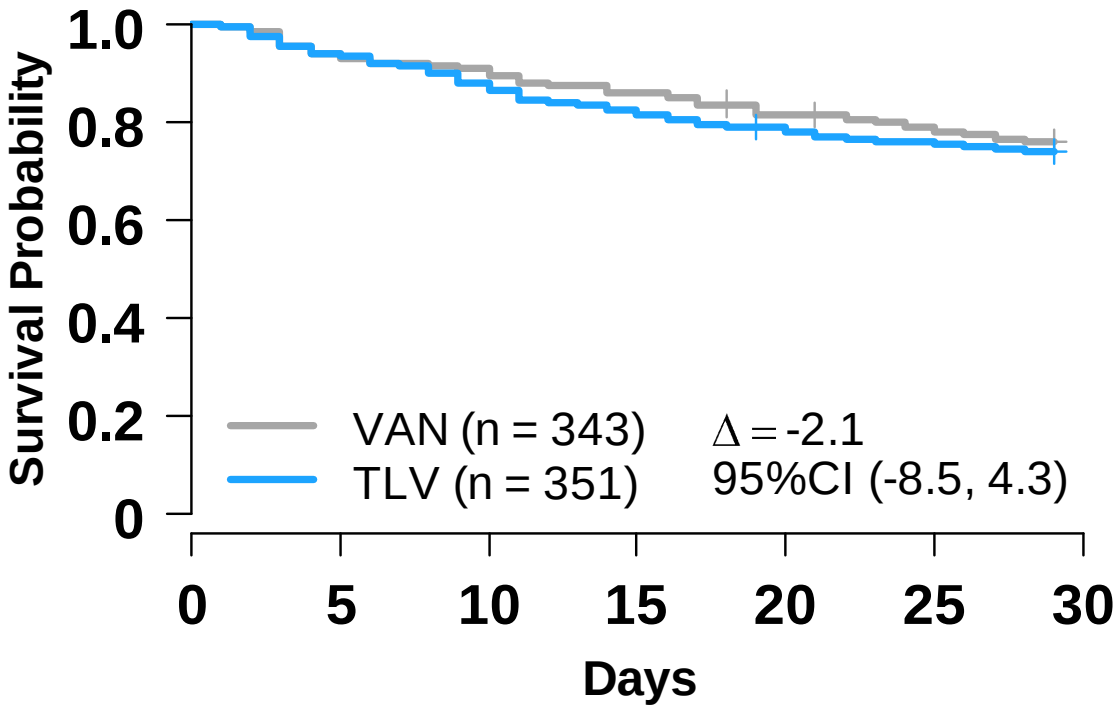
KM Survival Curves by Study
ATS/IDSA–AT Population





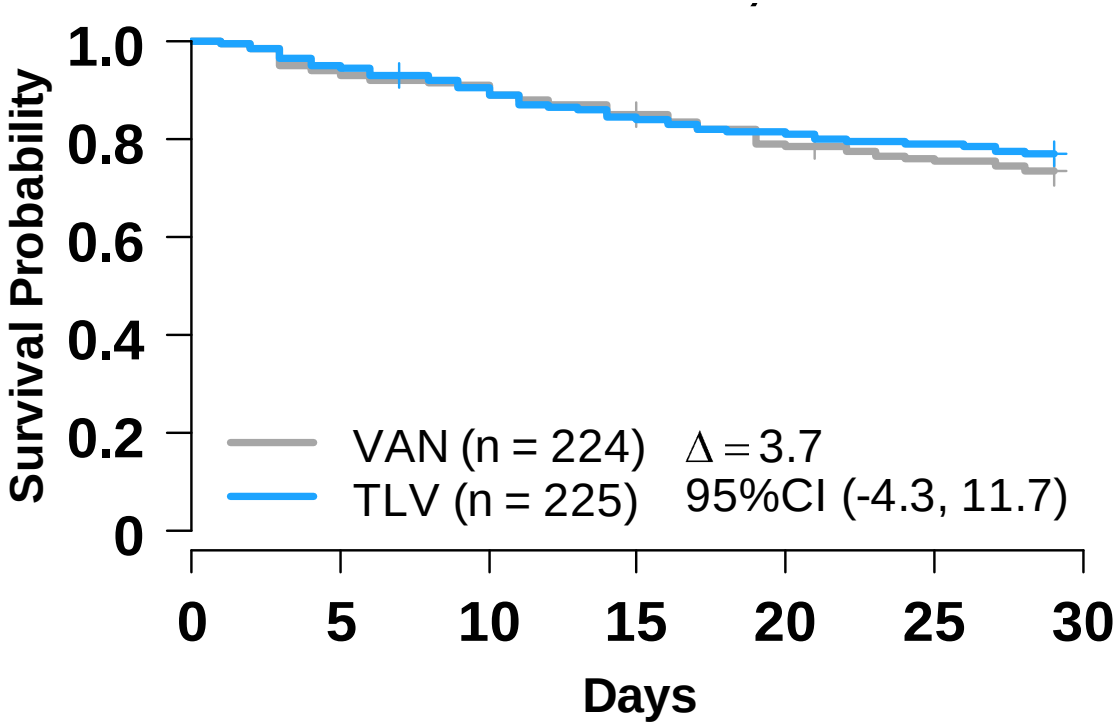
Noninferiority demonstrated in both studies

KM Survival Curves
ATS/IDSA–PP Population (Studies 0015, 0019)



PP = Per Protocol = Patients with at least 1 Gram(+) organism at Study Entry.

KM Survival Curves
ATS/IDSA–MPP Population (Studies 0015, 0019)



MPP = Modified Per Protocol = Patients with only Gram(+) organisms at Study Entry.

Efficacy Summary and Conclusions

TLV non-inferior to VAN in treatment of NP

- **Prospective analysis of clinical cure rates**
  - **Higher TLV cure rates in:**
    - **Monomicrobial *S. aureus* infections**
    - ***S. aureus* infections with higher MIC to VAN**
    - **Subgroups of clinical interest (e.g. bacteremic, elderly, high APACHE II score)**
- **Post hoc analyses of all-cause mortality**
  - **ATS/IDSA-AT (Study 0015 and Study 0019)**
  - **ATS/IDSA-PP (Gram(+), including mixed)**
  - **ATS/IDSA-MPP (Gram(+) only)**

Agenda

Introduction	Rebecca Coleman, PharmD *VP, Regulatory Affairs & Quality* *Theravance, Inc.*
Medical Need	Marin Kollef, MD *Professor of Medicine, Pulmonary and Critical Care* *Washington University, St. Louis*
Efficacy	Steven Barriere, PharmD *VP, Clinical & Medical Affairs* *Theravance, Inc.*
Safety	**Mathai Mammen, MD, PhD** **SVP, Research and Early Clinical Development** ***Theravance, Inc.***
Benefit Risk	Louis Saravolatz, MD *Professor of Medicine, Infectious Diseases* *St. John Hospital, Detroit*
Conclusion	Steven Barriere, PharmD *Theravance, Inc.*

Safety

Mathai Mammen, MD, PhD

Senior Vice President

Research and Early Clinical Development

Theravance, Inc.

Outline

- Exposure to TLV
- Safety Population
- Overview of Treatment-Emergent Adverse Events
- Areas of Special Interest
  - Renal Safety
  - All-Cause Mortality
- Post-Marketing Experience
- Summary and Recommendations

Exposure to Telavancin

Exposures	Patients, n
NP	751
cSSSI	1,029
Post-marketing	~125,000

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Adverse Event Overview
Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 751	VAN N = 752
Any AE	616 (82)	613 (82)
Any SAE	234 (31)	197 (26)
Possibly drug-related	23 (3)	17 (2)
Discontinuation due to AE	60 (8)	40 (5)

Most Common AEs (≥ 5% in Either Group)
Safety Population (Studies 0015, 0019)

	% Patients*	
	TLV N = 751	VAN N = 752
Diarrhea	11	12
Anemia	9	11
Constipation	9	9
Hypokalemia	8	11
Hypotension	6	7
Insomnia	5	6
Decubitus ulcer	5	6
Peripheral edema	5	5
Vomiting	5	4
Nausea	5	4
Acute renal failure	5	4
Atrial fibrillation	4	5

* A patient could have multiple events

SAEs Occurring in ≥ 1% in Either Group
Safety Population (Studies 0015, 0019)

	Patients*, n (%)	
	TLV N = 751	VAN N = 752
Septic shock	30 (4)	28 (4)
Multiorgan failure	24 (3)	14 (2)
Respiratory failure	21 (3)	22 (3)
Acute renal failure	18 (2)	11 (1)
Sepsis	12 (2)	9 (1)
Nosocomial pneumonia	10 (1)	14 (2)
Congestive heart failure	4 (<1)	10 (1)
Acute respiratory failure	4 (<1)	8 (1)

* A patient could have multiple events

AEs Resulting in Drug Discontinuation Occurring in ≥ 3 Patients in Either Group

Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 751	VAN N = 752
Renal events*	14 (2)	7 (1)
QTc interval prolonged	8 (1)	2 (< 1)
Core reading lab	3 (< 1)	0
Sepsis / septic shock	4 (< 1)	6 (< 1)
Multiorgan failure	1 (< 1)	4 (< 1)

* Renal events = acute renal failure, worsening of chronic renal failure, renal insufficiency, renal impairment, and increased serum creatinine

Cardiac AEs Occurring in ≥ 2% in Either Group
Safety Population (Studies 0015, 0019)

Cardiac events	Patients, n (%) TLV N = 751	Patients, n (%) VAN N = 752
Atrial fibrillation	31 (4)	36 (5)
Bradycardia	11 (1)	16 (2)
Cardiac failure congestive	19 (3)	24 (3)
Tachycardia	17 (2)	16 (2)
Ventricular tachycardia	1 (<1)	12 (2)

Safety in Patient Subgroups

- No apparent differences in AEs or SAEs in both treatment groups across the following patient subgroups
  - Sex
  - Weight / Body Mass Index
  - Race
- Higher rates of AEs for elderly (≥ 65 yo) and diabetics, but similar between treatment groups
- Higher rates of renal AEs for TLV group in those with pre-existing renal risk factors

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Renal AEs and Laboratory Abnormalities
Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 751	VAN N = 752
Renal AEs	74 (10)	57 (8)
Renal SAEs	26 (3)	16 (2)
Creatinine increase > 1.5× baseline	143 (19)	97 (13)

Renal AE = acute renal failure, worsening of chronic renal failure, renal insufficiency, renal impairment, and increased serum creatinine

Resolution of Renal AEs Leading to Discontinuation – Safety Population (Studies 0015, 0019)

	Patients, n	
	TLV N = 14	VAN N = 7
Death	0	1
Recovered or improving	11	2
Condition present and unchanged	3	4

Renal Summary

- More nephrotoxicity observed on TLV than VAN
  - Renal AEs, SAEs
  - Rise in serum creatinine
  - Sensitivity to adverse renal experience for patients with pre-existing renal risk factors
  - Resolution comparable
- Observations of renal effects consistent with cSSSI P3 trials

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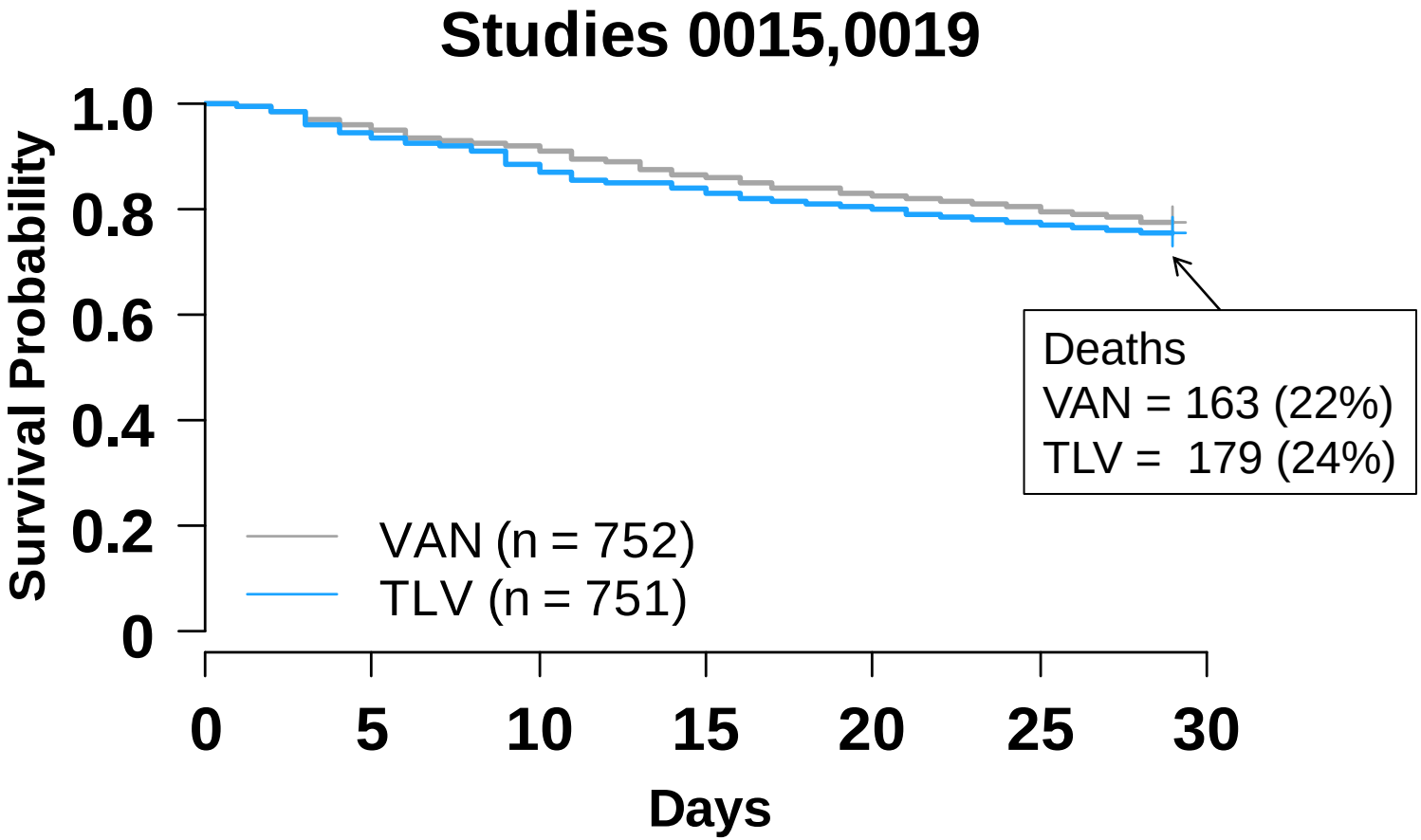
28-Day All-Cause Mortality (Survival)
Safety Population



Cause of Death
Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 751	VAN N = 752
Respiratory related (non-NP)	28 (4)	28 (4)
NP	22 (3)	27 (4)
Fungus / non-respiratory infection	5 (1)	3 (< 1)
Sepsis / shock	38 (5)	30 (4)
Multiorgan failure	19 (3)	8 (1)
Renal-related	4 (1)	2 (< 1)
Cardiac / cerebrovascular	40 (5)	44 (6)
Unknown cause	14 (2)	10 (1)
Other	5 (1)	6 (1)
Gastrointestinal	4 (1)	5 (1)
Total Deaths by Day 28	179 (24)	163 (22)

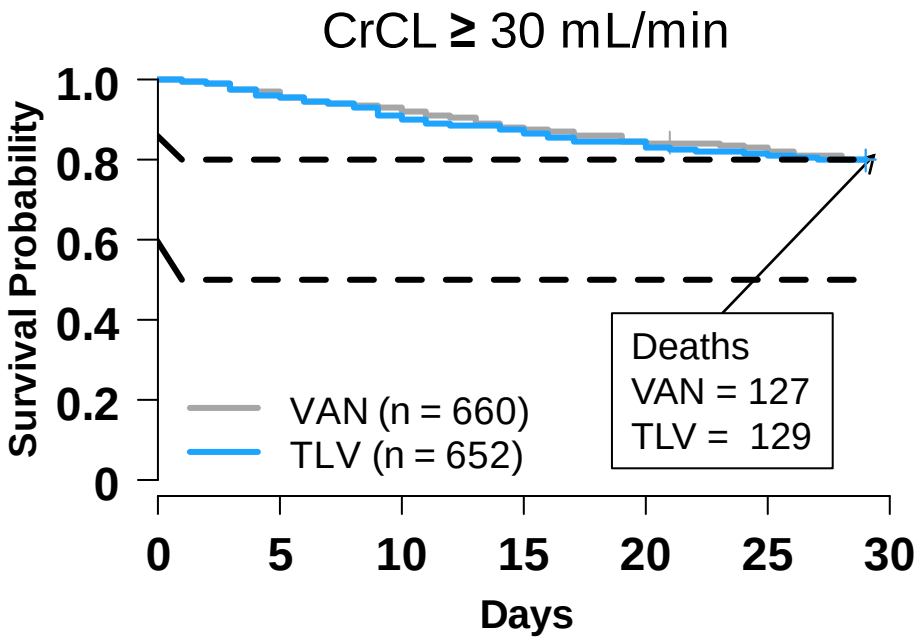
Investigation of Mortality

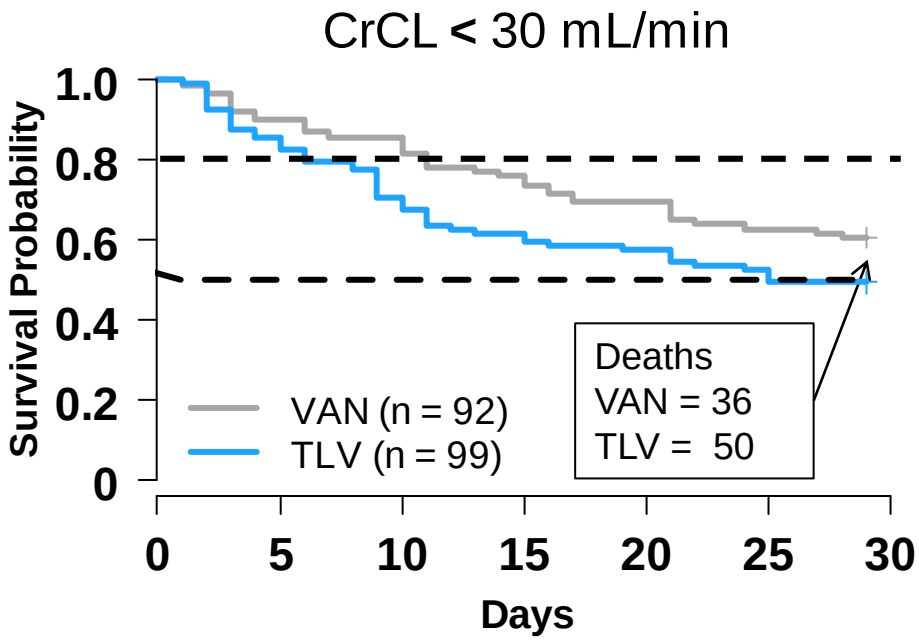
- Intensive and comprehensive statistical analysis
  - Cox proportional hazard models and decision tree methods
- Methods
  - Identify all factors associated with mortality without influence from treatment
  - Identify factors common to both studies
  - Identify treatment interactions with prognostic factors

Results of Statistical Analysis

- Multiple prognostic factors identified
- Treatment interaction with baseline eCrCL accounted for almost all variance in mortality rates
- TLV patients with eCrCL < 30mL/min had a higher rate of mortality than VAN patients
- TLV patients with eCrCL ≥ 30mL/min had a similar rate of mortality to VAN patients
  - No by-treatment interactions or increased mortality risk with diabetes, CHF, or age

28-Day All-Cause Mortality by Baseline CrCL
Safety Population (Studies 0015, 0019)





Further Investigations for Patients with Baseline CrCL < 30 mL/min

- Hypotheses explored in this group
  - Underlying baseline comorbid conditions
  - Resistant Gram(-) infections
  - Over-exposure to TLV
  - Nephrotoxicity

Cause of Death for Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 99	VAN N = 92
Sepsis / shock	8 (8)	9 (10)
Multiorgan failure	10 (10)	3 (3)
Renal-related	2 (2)	0
Respiratory related (non-NP)	11 (11)	7 (8)
NP	6 (6)	5 (5)
Fungus / non-respiratory infection	1 (1)	0
Cardiac / cerebrovascular	8 (8)	8 (9)
Unknown cause	3 (3)	3 (3)
Other	2 (2)	1 (1)
Gastrointestinal	1 (1)	0
Total Deaths	50 (51)	36 (39)

MOF Deaths in VAN Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

Baseline Pathogen	Day of death	Baseline Condition / Comments
MRSA (S)	D6	Withdrew consent D4
MSSA (S)	D10	Persistent bacteremia to D3
None, *C. albicans* D7	D21	Sepsis D8 onward

MOF = Multiorgan failure

Baseline Condition of MOF Deaths in TLV Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

Baseline Pathogen(s)	Day of Death	Baseline Condition / Comments
None	D2	Frostbite/exposure, left ventricular dysfunction
MRSA (S TLV)	D2	ARF on CRF, COPD, CHF, pulmonary edema, DM, s/p MI with CABG & pacemaker
***P. aeruginosa* (R AZT)**	**D3**	**CVA, ICH, ARF**
None	**D3**	**CVA, CRF**
MSSA (S), *E. coli* (S AZT)	D7	CHF, COPD, DM; DC TLV AE, 5d amox/clav, meropenem
Acinetobacter (I P/T)	**D8**	**ARF**
Yeast	D9	ARF on CRF, ARDS, MI, CVA, hypotension, hemorrhagic shock
P. aeruginosa (R AZT)	D11	CRF, CHF, respiratory failure
MSSA (S TLV)	D12	Head trauma, SAH, subdural hematoma, ARF
None; Acinetobacter D6 (R AZT)	D19	ARF, CVA, respiratory failure

MOF = Multiorgan failure; ARF = acute renal failure; CRF = chronic renal failure; SAH = subarachnoid hemorrhage.

Cause of Death for Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 99	VAN N = 92
Sepsis / shock	8 (8)	9 (10)
Multiorgan failure	10 (10)	3 (3)
Renal-related	2 (2)	0
Respiratory related (non-NP)	11 (11)	7 (8)
NP	6 (6)	5 (5)
Fungus / non-respiratory infection	1 (1)	0
Cardiac / cerebrovascular	8 (8)	8 (9)
Unknown cause	3 (3)	3 (3)
Other	2 (2)	1 (1)
Gastrointestinal	1 (1)	0
Total Deaths	50 (51)	36 (39)

Renal-Related Deaths in TLV Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

Baseline Pathogen	Day of Death	Baseline Condition / Comments
MRSA (S TLV)	D4	Chemo (lymphoma), malnutrition, withdrew consent D3
Acinetobacter (MDR)	D9	CRF, DM, s/p MI with LVD and pacemaker; colistin started D3, renal function worsened D4

Deaths with Resistant Gram(-) Pathogens in TLV Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

Baseline Pathogen(s)	Day of Death	Baseline Condition / Comments
P. aeruginosa (R AZT)	D3	CVA, ICH, ARF
Acinetobacter (I P/T)	D8	ARF
Acinetobacter (MDR)	D9	CRF, DM, s/p MI with LVD and pacemaker; colistin started D3, renal function worsened D4
P. aeruginosa (R AZT)	D11	CRF, CHF, respiratory failure
None; Acinetobacter D6 (R AZT)	D19	ARF, CVA, respiratory failure

- 5 patients had resistant Gram(-) pathogens
  - Adequacy of Gram(-) coverage investigated

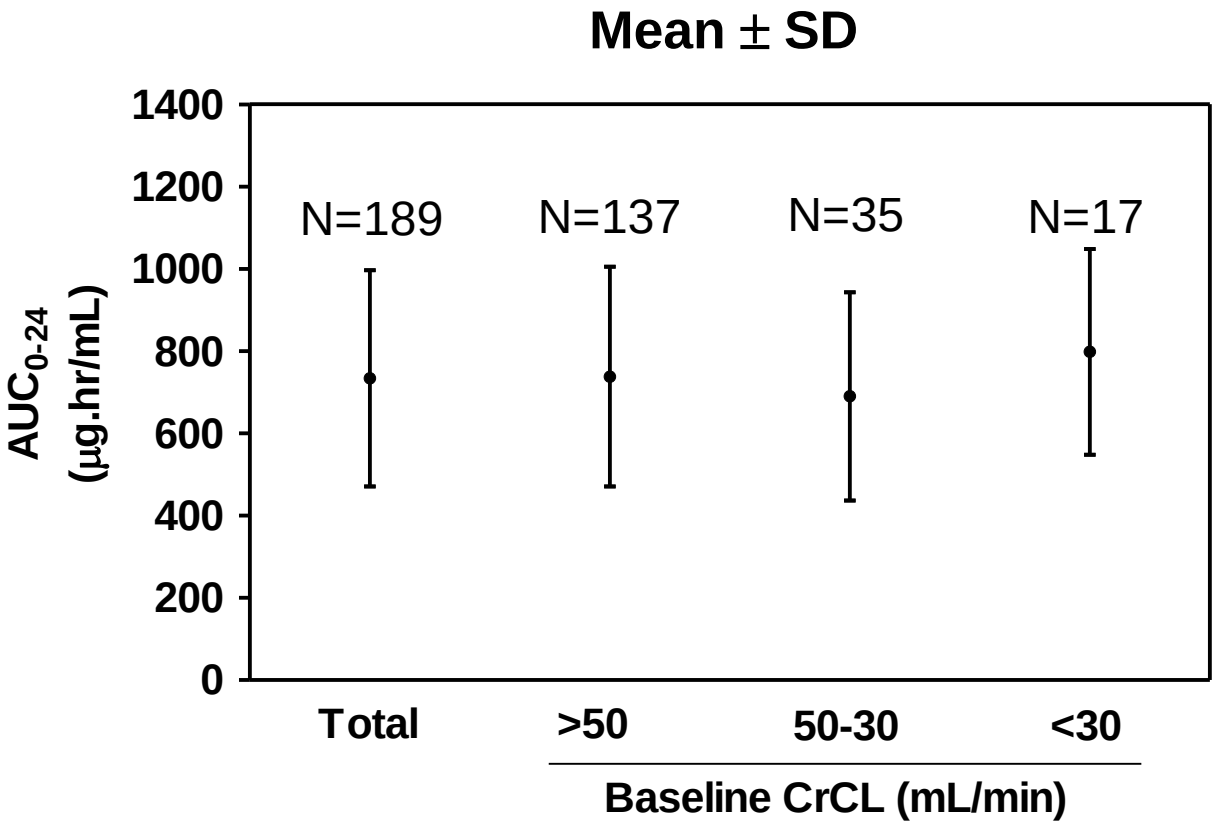
Gram(-) Infections Confound All-Cause Mortality Analysis in Patients with Baseline CrCL < 30 mL/min

Safety Population (Studies 0015, 0019)

	N		Deaths, n	
	TLV	VAN	TLV	VAN
Baseline CrCL < 30 mL/min patients	99	92	50	36
			Δ = 14	
Excluding Gram(-) only infections with inadequate Gram(-) coverage patients	85	81	40	33
			Δ = 7	
Excluding both Gram(-) only AND mixed infections with inadequate Gram(-) coverage patients	77	75	35	32
			Δ = 3	

Telavancin Exposure (AUC_{0-24}) in Patients with Normal and Impaired Renal Function

PK Population (Studies 0015, 0019)



All-Cause Mortality: Summary

- **Baseline CrCL ≥ 30 mL/min (87% of population)**
  - **Number of deaths similar on TLV and VAN**
- **Baseline CrCL < 30 mL/min (13% of population)**
  - **Number of deaths on TLV greater than on VAN**
  - **Underlying comorbid conditions** ***YES***
  - **Resistant Gram(-) infections** ***POSSIBLY***
  - **Over-exposure to TLV** ***NO***
  - **Nephrotoxicity** ***POSSIBLY***
- **CrCL of 30 mL/min is the appropriate threshold for caution (baseline, on-treatment)**

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Most Commonly Reported Post-Approval Adverse Events

- Estimated 125,000 patients treated
- 265 reports as of 10/1/12

Adverse event	n
Blood creatinine increased	20
Renal failure acute	17
Renal failure	15
Renal impairment	8
Rash	20
Urticaria	6
Pruritis	5
Hypersensitivity	5
Nausea	30
Dysgeusia	17
Chills	15
Pyrexia	12
Dyspnea	8
INR increased	7
Urine abnormality (foamy urine)	6
Back pain	6
Thrombocytopenia	5

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Summary of Safety

- AEs and SAEs
  - Overall rates of AEs similar
  - SAEs and DCs more frequent on TLV
  - No cardiac safety signal relative to VAN
- Areas of Special Interest
  - More evidence of nephrotoxicity on TLV
  - More deaths on TLV in patients with severe renal insufficiency
- High level of consistency of safety findings across P3 NP, P3 cSSSI and post-marketing experience

Recommendations

- Serum creatinine (CrCL) should guide therapy
  - CrCL should be obtained prior to initiation of treatment and during treatment
    - Adjust dose accordingly
  - If baseline CrCL < 30 mL/min, or if on-treatment CrCL falls below 30 mL/min, use TLV only if anticipated benefit outweighs potential risk
- REMS plan focused on communicating the mortality risk in patients with CrCL < 30mL/min

Agenda

Introduction	Rebecca Coleman, PharmD *VP, Regulatory Affairs & Quality* *Theravance, Inc.*
Medical Need	Marin Kollef, MD *Professor of Medicine, Pulmonary and Critical Care* *Washington University, St. Louis*
Efficacy	Steven Barriere, PharmD *VP, Clinical & Medical Affairs* *Theravance, Inc.*
Safety	Mathai Mammen, MD, PhD SVP, Research and Early Clinical Development *Theravance, Inc.*
Benefit Risk	**Louis Saravolatz, MD** ***Professor of Medicine, Infectious Diseases*** ***St. John Hospital, Detroit***
Conclusion	Steven Barriere, PharmD *Theravance, Inc.*

Benefit/Risk

Louis D. Saravolatz, MD, MACP

St. John Hospital, Detroit, MI

Increasing Burden of NP Due to Known or Suspected MRSA

- Over 50% of *S. aureus* infections are MRSA; among most common NP pathogens
- Treatment of NP is increasingly difficult
  - Significant clinical impact / burden
  - Treatment failure rates remain high as does all cause mortality (20 - 50%)
- Paucity of current treatment options limited by emerging resistance, toxicity

We need new effective antibiotics for our patients with NP, especially when MRSA is known or suspected

Individualization of Care

- Determine severity of infection
- Cover likely pathogens with empiric therapy
  - Patient history
  - Local epidemiology
- Assess comorbid conditions
- Choose appropriate therapy and dose
- Monitor for efficacy and safety
  - Reassess after obtaining microbiology results

Benefit / Risk assessment made at the individual patient level

Telavancin – Key Features

- Activity against strains resistant to other drugs
- Dual mechanism of action
- Low potential for development of resistance
- Bactericidal
- Penetration into lung
  - Not inactivated by surfactant
- Once daily dosing

Telavancin – Benefits (1)

- **TLV is effective in the treatment of nosocomial pneumonia, including ventilator assisted pneumonia**
  - **Clinically relevant results**
    - **Largest nosocomial pneumonia studies, and drawn from a broad population of patients with multiple comorbid conditions**
- **No emergence of resistance to date**

Telavancin – Benefits (2)

- **Active against strains with reduced susceptibility**
  - ***S. aureus* infections with VAN MIC ≥ 1 µg/mL**
  - **VISA, hVISA strains susceptible to TLV**
  - **LZD-resistant strains susceptible to TLV**
- **Effective in more difficult to treat nosocomial pneumonia patients**
  - **Bacteremic**
  - **High APACHE II score**

Telavancin – Manageable Risks

- All-cause mortality in patients with severe renal impairment
  - Unclear mechanism, multiple confounders
  - Consider benefit/risk in treating patients with baseline, or on treatment CrCL < 30 mL/min
- Nephrotoxicity
  - Monitor creatinine (as labeled)
- QTc prolongation
  - Use with caution in patients at risk (as labeled)
- Pregnancy category C (potential fetal risk)
  - Avoid use in pregnancy (as labeled)

Primary Treatment Considerations

- Early effective empiric therapy in NP that provides coverage against likely pathogens
  - TLV has activity against MRSA, MSSA, hVISA / VISA, and PRSP
  - Ensure adequate Gram(-) coverage
- Understand the patient's baseline comorbid conditions, including renal function

Telavancin Candidate (1)

- 75 y.o. female nursing home resident with COPD had been hospitalized for an exacerbation and treated with antibiotics (levofloxacin) within the last month. History of diabetes mellitus with peripheral neuropathy, and CAD
- Patient complained of cough and shortness of breath for two days
  - T = 38.3°C, P = 110, RR = 28, BP = 105 / 76
  - Lung: rales and bronchial breath sounds on left
- Chest X-ray: left lower lobe consolidation
- Sputum Gram stain: numerous PMN's, Gram(+) cocci
  - Hospital epidemiology: Significant rate of VAN MIC ≥ 1
- CrCL = 44 mL/min, WBC = 2,800, Platelets = 45,000

Telavancin Candidate (2)

- 57 y.o. female with lung cancer was admitted with trauma. After surgical intervention, she remained ventilator dependent
- On the 4th hospital day she developed fever (39.6°C) and new infiltrates.
  - WBC = 9,200, 21% bands, SCr = 0.6, CrCL = 96 mL/min
  - ETA: few epis, Gram(+) cocci, MRSA VAN MIC = 1.5 µg/mL
- Meds: Paroxetine, trazodone for depression
- Diagnosis: VAP due to MRSA
- Outcome: Treated with vancomycin but expired on 10th hospital day

Summary

- Increasing burden of NP due to MRSA
- Paucity of treatment options (VAN, LZD) in the face of emerging resistance and toxicity
- TLV has positive benefit / risk profile

Patients with nosocomial pneumonia need telavancin as a treatment option

Agenda

Introductions	Rebecca Coleman, PharmD *VP, Regulatory Affairs & Quality* *Theravance, Inc*
Medical Need	Marin Kollef, MD *Professor of Medicine, Pulmonary and Critical Care* *Washington University, St. Louis*
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Safety	Mathai Mammen, MD, PhD *SVP, Research and Early Clinical Development* *Theravance, Inc*
Benefit Risk	Louis Saravolatz, MD *Professor of Medicine, Infectious Diseases* *St. John Hospital, Detroit*
Conclusion	**Steven Barriere, PharmD** ***Theravance, Inc***

Conclusions

Conclusions

- Significant unmet medical need in NP
- TLV is active against Gram(+) pathogens, including MRSA, that are non-susceptible to other agents
  - Low potential for emergence of resistance
- Risk of nephrotoxicity is recognized, consistent with cSSSI and post-marketing experience, and manageable
- Risk of increased mortality in patients with severe renal impairment and among patients whose renal function deteriorates on treatment
- TLV has demonstrated efficacy in NP in a large clinical program

Proposed Indication

- **VIBATIV® (telavancin) is indicated for the treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP), caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates) or *Streptococcus pneumoniae***

Advisors

G. Ralph Corey, MD	***Professor of Medicine, Infectious Diseases*** ***Duke University Medical Center***
Ethan Rubinstein, MD	***Professor, Head of Infectious Diseases*** ***University of Manitoba***
Andrew Shorr, MD	***Associate Director, Pulmonary and Critical Care*** ***Washington Hospital Center***
Jamie Dwyer, MD	***Assistant Professor, Division of Nephrology*** ***Vanderbilt University Medical Center***
Gary Koch, PhD	***Professor of Biostatistics*** ***University of North Carolina, Chapel Hill***
Anthony Scialli, MD	***Senior Scientist, Developmental Toxicology*** ***Tetra Tech, Inc.***

Supporting Slides

Population Definitions

THRX Name	FDA Name	Definition
Safety	AT Safety	All patients in AT population, but 2 patients randomized to VAN received TLV and are included as TLV
ATS/IDSA–AT	AT - ATS/IDSA	All patients in AT population meeting ATS/IDSA criteria
Per-Protocol (PP)	MAT – Gram^{+}	All patients in AT population with at least 1 Gram(+) organism at baseline
Modified Per-Protocol (MPP)	—	All patients in AT population with only Gram(+) organisms at baseline
MRSA	Same	All patients in AT population with MRSA at baseline
MMRSA	—	All patients in AT population with only MRSA at baseline

Vancomycin C_{trough} PK Population (Studies 0015, 0019)

- Decision to obtain a serum sample for VAN trough determination was taken at the site and samples were analyzed at that site
- Results were captured by a CRF

C_{trough} (µg/mL)	Mean ± SD n = 226
Initial	12 ± 6
Average	13 ± 6

CRF = case report form

Vancomycin C_{trough} vs. Clinical Response - PK Population (Studies 0015, 0019)

Clinical Response	C_{trough} (µg/mL) Mean ± SD (n)	
	Initial	Average
Cured	11 ± 5 (136)	12 ± 6 (136)
Indeterminate	13 ± 6 (29)	15 ± 5 (29)
Failed	13 ± 9 (42)	14 ± 7 (42)

Between Study Differences
AT Population

	Patients, n (%)		Difference
	0015 N = 746	0019 N = 757	0015 – 0019 n (% of AT)
Compromised immunity	11 (1)	34 (4)	-23 (2)
Entry post surgical operation	520 (70)	440 (58)	80 (5)
Mixed infection	95 (13)	175 (23)	-80 (5)
Pseudomonas or *Acinetobacter* or *Stenotrophomonas* infection	125 (17)	208 (27)	-83 (6)
Prior treatment failure	174 (23)	252 (33)	-78 (5)
ARDS or ALI	97 (13)	50 (7)	47 (3)
BMI ≥ 40	36 (5)	11 (1)	25 (2)
Con-meds w/risk of Torsades	425 (57)	342 (45)	83 (6)
History of diabetes	232 (31)	162 (21)	70 (5)
Geographic region	401 (54)	222 (29)	179 (12)
Gender: Female vs. Male	298 (40)	249 (33)	49 (3)
CrCL < 30 mL/min	112 (15)	79 (10)	33 (2)
Comorbidities > 2	434 (58)	391 (52)	43 (3)
Race: White vs. Others	539 (72)	502 (66)	37 (2)
Hemodialysis	20 (3)	8 (1)	12 (1)

ARDS = acute respiratory distress syndrome, ALI = acute lung injury

Cure Rates by Renal Function
CE Population (Studies 0015, 0019)

CrCL Category	N	% Cure TLV	% Cure VAN	Difference TLV - VAN (95% CI)
< 30 (severe)	58	82.6	71.4	11.2 (-11.8, 31.2)
30 - 50 (moderate)	127	77.6	82.6	-5.0 (-19.0, 8.9)
50 - 80 (mild)	163	82.1	80.0	2.1 (-10.0, 14.1)
> 80 (normal)	306	84.3	82.4	2.0 (-6.4, 10.3)

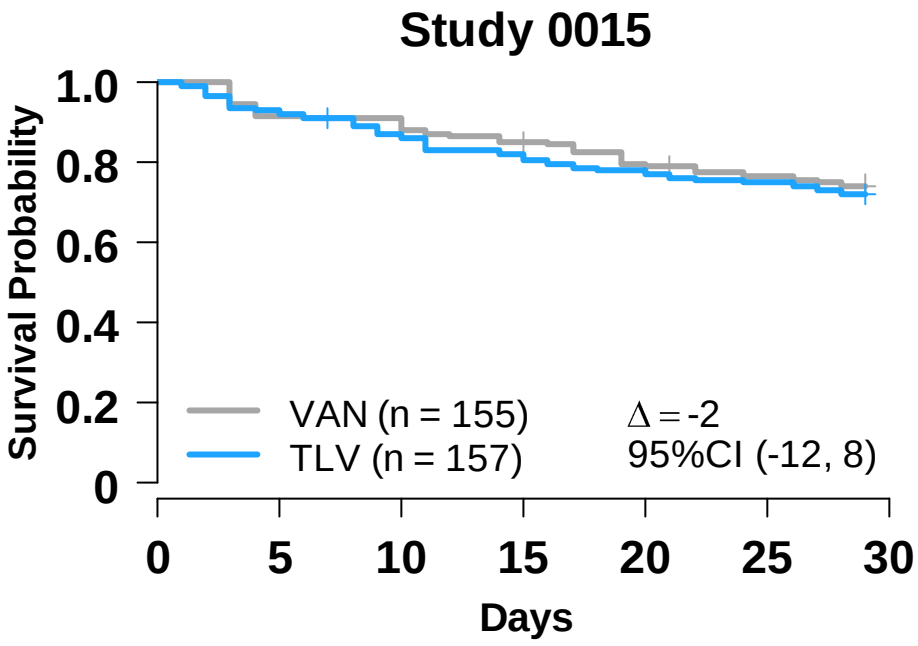
- Population selected to reveal true drug effects; excludes potentially effective antibiotics and excludes pure Gram(-) infections

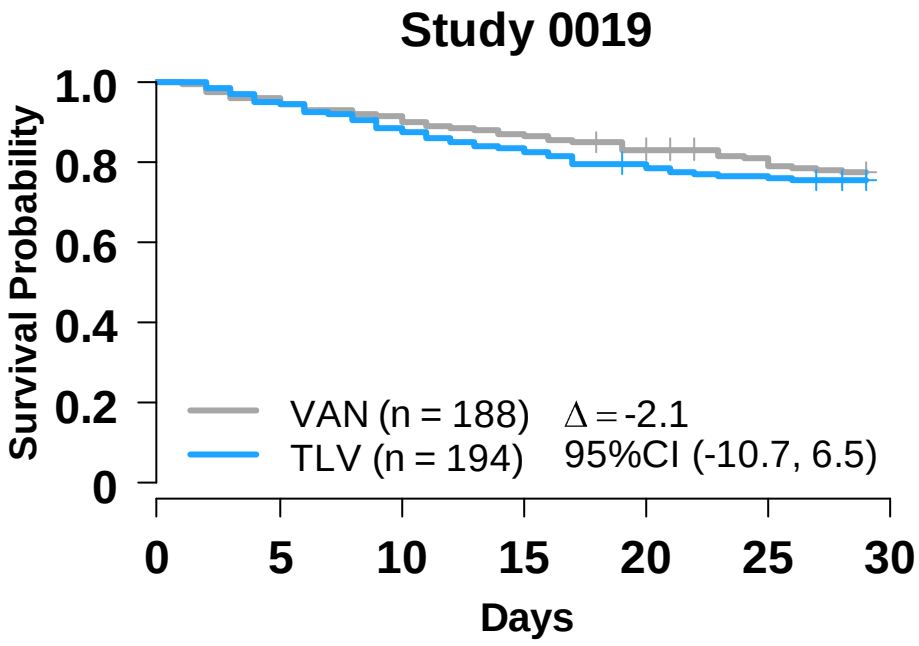
Cure Rates by Renal Function
AT Population (Studies 0015, 0019)

CrCL Category	N	% Cure		Difference TLV - VAN (95% CI)
		TLV	VAN	
< 30 (severe)	191	38.4	47.8	-9.4 (-23.4, 4.6)
30 - 50 (moderate)	293	54.2	58.9	-4.7 (-16.1, 6.6)
50 - 80 (mild)	362	59.2	61.8	-2.6 (-12.6, 7.5)
> 80 (normal)	657	67.0	61.9	5.1 (-2.2, 12.4)

- Includes patients with pure Gram(-) and mixed, potentially inadequately treated Gram(-) pathogens and other potentially confounding factors

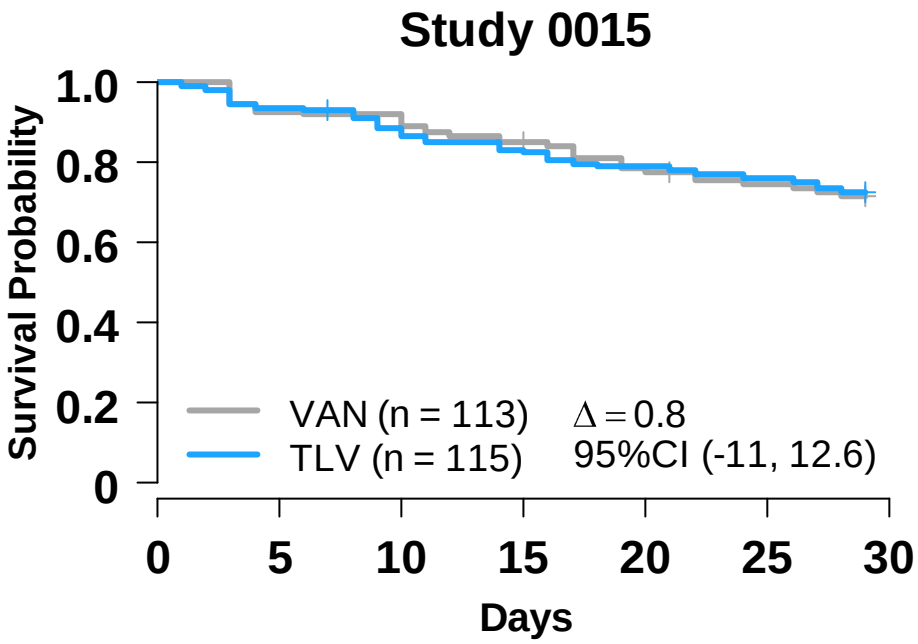
KM Survival Curves by Study
ATS/IDSA–PP Population

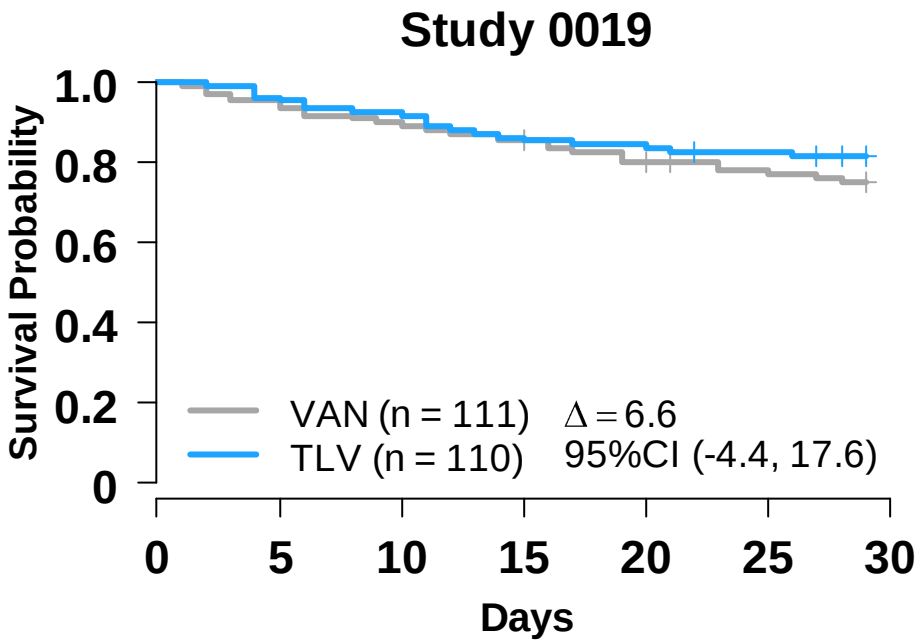




PP = Per-protocol = Patients with at least one Gram(+) organism at Study Entry.

KM Survival Curves by Study
ATS/IDSA–MPP Population





MPP = Modified Per-Protocol = Patients with only Gram(+) organisms at Study Entry.

“Cutpoints” in Renal Function are Based on Physiology

GFR (mL/min)	Labs	Repercussions
80 - 120	Normal	None
30 -80ish	Substances cleared by GFR (BUN, SCr)	CV risk, fatigue
10 - 30	Hgb, Hct, Ca, P, FGF-23	CV risk, fatigue, appetite
< 10	Many abnormal	CV risk, nausea, pruritus, appetite, taste

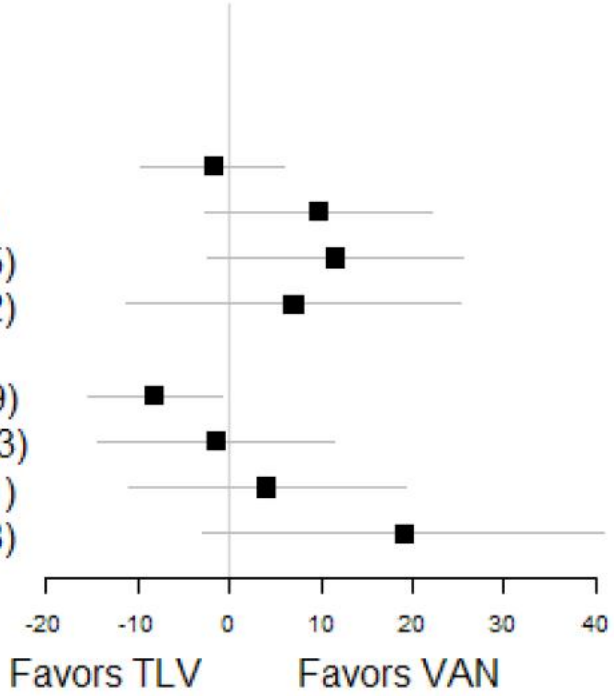
Dwyer 2012, after Emmett

Measures to Ensure Blinding at Sites

- **Blinding plans**
  - **To document the roles for blinded and unblinded staff and the responsible individuals**
    - **Blinded: patient identification, consent, screening, patient management and study assessments**
    - **Unblinded: randomization calls, drug preparation and blinding, vancomycin levels, dose adjustments**
  - **To identify separate procedures needed for vancomycin therapeutic levels (e.g., mechanism for maintaining results outside of medical chart)**
  - **Plan completed by each site, signed by investigator and reviewed by CROs or sponsor**

F5 pg30: 28-Day All-Cause Mortality (based on K-M estimates) by Baseline Creatinine Clearance (AT Population)

Study	Creatinine Clearance (mL/min)	Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
0015	>80	143	(12.2)	152	(14.1)	-1.8 (-9.6, 6.0)
	>50-80	88	(27.4)	88	(17.7)	9.7 (-2.7, 22.1)
	30-50	80	(34.7)	83	(23.1)	11.5 (-2.5, 25.5)
	<30	61	(44.3)	51	(37.3)	7.0 (-11.2, 25.2)
0019	>80	181	(10.5)	181	(18.7)	-8.2 (-15.5, -0.9)
	>50-80	96	(25.6)	90	(27.1)	-1.5 (-14.4, 11.3)
	30-50	62	(27.7)	68	(23.7)	4.0 (-11.1, 19.1)
	<30	38	(61.1)	41	(42.1)	19.0 (-2.9, 40.8)

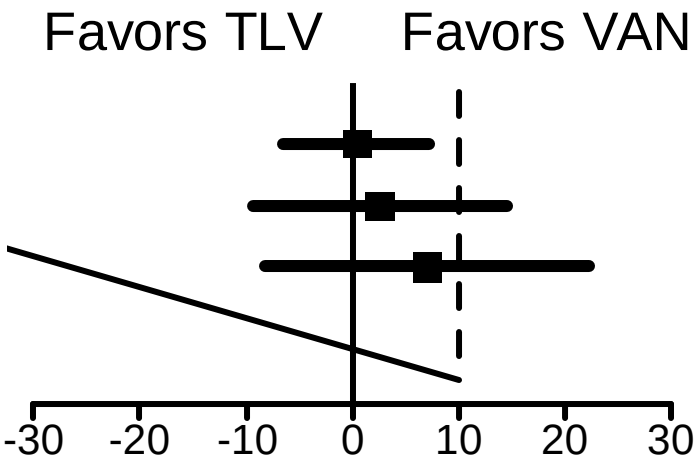


All-Cause Mortality (Survival) for Patients with No Decline to < 30 mL/min On-Treatment

Safety Population

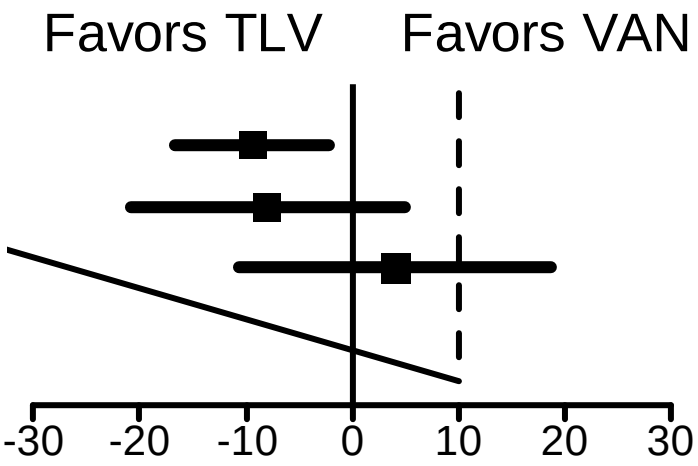
Study 0015

	N	Delta	95% CI
>80	282	0.4	(-7.9, 7.2)
>50-80	152	2.6	(-9.4, 14.5)
30-50	120	7.0	(-8.1, 22.2)



Study 0019

	N	Delta	95% CI
>80	347	-9.4	(-16.6, -2.2)
>50-80	160	-8.0	(-21, 4.9)
30-50	102	4.1	(-10.7, 18.8)



All-Cause Mortality for Patients by Baseline CrCL
Safety Population (Studies 0015, 0019)

	Patients, Deaths / N	
No Decline* < 30 mL/min	TLV	VAN
All ≥ 30	79 / 564	99 / 599
> 80	30 / 310	47 / 319
50 - 80	26 / 150	32 / 162
30 - 50	23 / 104	20 / 118
< 30 (Reference)	50 / 99	36 / 92

Developmental Findings in Rat, Rabbit, and Minipig

- **Rat (Segment II) Study**
  - Single fetuses with shortened limb at 100 mg/kg/day (1/332) and 150 mg/kg/day (1/322)
  - Neither confirmed during skeletal examination
  - Decrement in fetal body weights
- **Rat (Segment III) Study**
  - One pup with transient limited use of limb at 150 mg/kg/day
- **Rabbit (Segment II) Study**
  - Single fetus with shortened limb at 75 mg/kg/day (1/156)
  - Same fetus multiply malformed
- **Minipig (Segment II) Study**
  - No limb defects at high dose
  - Control, low, and mid-dose groups with polydactyly
  - Absent radius in single fetus in mid-dose group
- **Findings in all studies observed in historical control data**

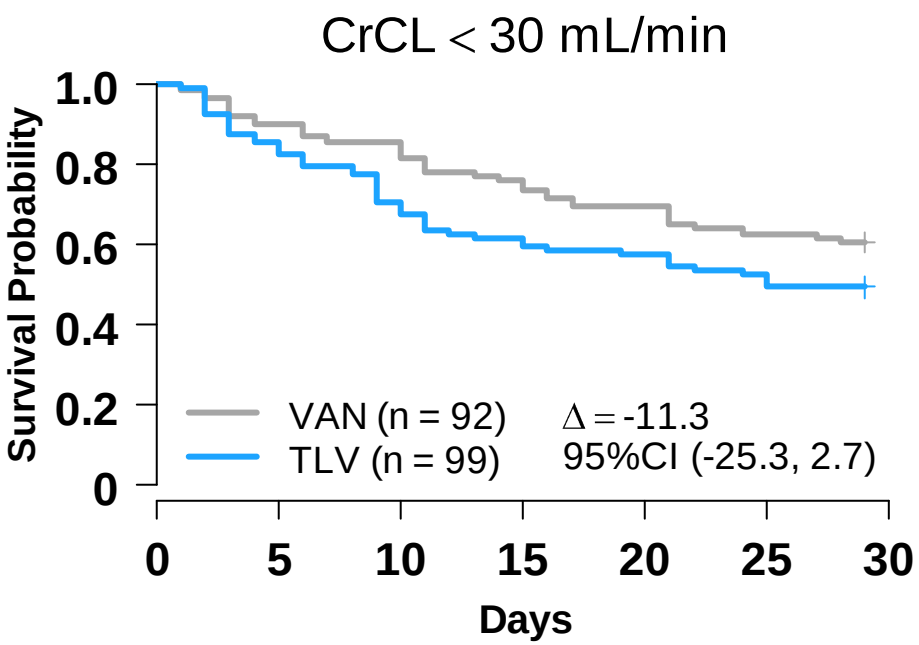
Pre- and Post-Natal Development Study (Segment 3) in Rats

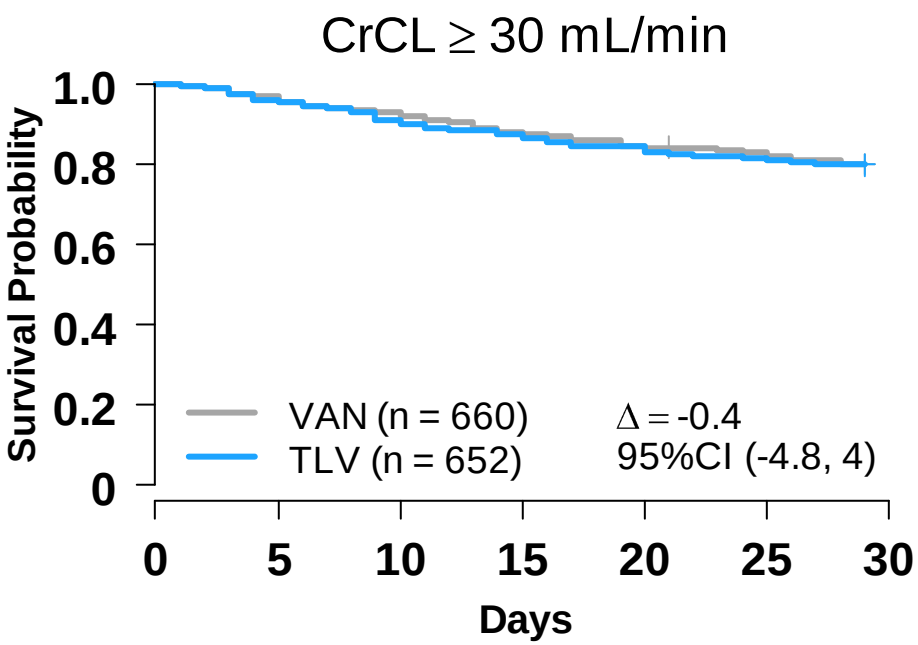
Dose (mg/kg/day)	LD4 (post cull)	LD6	LD7	LD14	LD21
0 (D5W)	0 / 176	0 / 176	0 / 176	0 / 176	0 / 175
0 (placebo)	0 / 167	0 / 166	0 / 166	0 / 166	0 / 166
50	0 / 192	0 / 192	0 / 192	0 / 184	0 / 184
100	0 / 192	0 / 192	0 / 192	0 / 192	0 / 192
150	0 / 177	1 / 176	1 / 176	0 / 176	0 / 175

- Doses of 50, 100 or 150 mg/kg/day on gestation days 6 through LD21
- No limb defects in F1 generation pups
- "…pup with transient (LD6 and 7) limited use of a forelimb…"

LD = lactation day

All-Cause Mortality (Survival) by Baseline CrCL
Safety Population (Studies 0015, 0019)





Safety Population: 2 patients randomized to VAN but received TLV

Resistance Studies

Clinical and in vitro studies suggest a low potential to select for resistance

- Clinical
  - No resistance detected during Phase 2 and Phase 3 cSSSI studies
  - No resistance detected during Phase 3 NP studies
  - No resistance detected in surveillance or clinical use
- In vitro
  - Single-step selection studies failed to detect resistance
  - Multipassage selection studies identified a single clone with an MIC elevated 8× the parental MIC after 43 days

Characterization of a Multipassage-Selected MRSA Clone

- **Altered susceptibility**

Isolate	MIC (µg/mL) TLV	VAN	DAP
SA248	0.12	0.5	1
SA248/p43	1	2	2

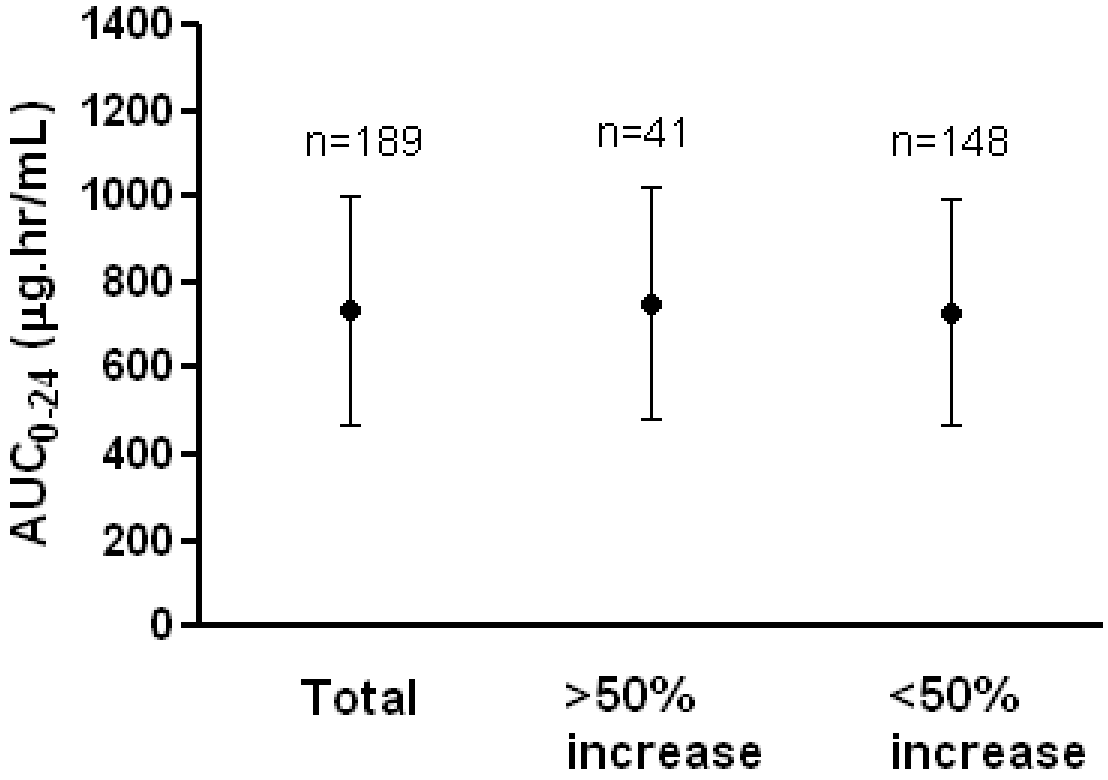
- **Reduced in vitro fitness**
- **Altered cell envelope**
  - Thickened cell wall, reduced autolytic activity
  - Altered fatty acid composition; increased membrane fluidity
- **Extensive changes in the genome and transcriptome**
  - 148 nucleotide alterations
  - >600 genes up- or down-regulated ≥2×
    - Cofactor biosynthesis, cell wall-related genes, fatty acid biosynthesis, regulatory functions (*agr*)

Song Y, et al. *Microb Drug Resist.* (in press)

Telavancin AUC_{0-24} vs. ≥ 50% Increase from Baseline in Serum Creatinine

PK Population (Studies 0015, 0019)

Mean ± SD



Reported Post-Marketing AEs—Deaths

- 8 deaths reported
  - 1 patient with h/o diabetes, juvenile rheumatoid arthritis, coronary artery disease developed MRSA vertebral osteomyelitis, bacteremia, and acute renal failure requiring hemodialysis. Pneumonia also occurred with subsequent multiple organ dysfunction syndrome, development of cavitary pneumonia and death
    - Events reported as possibly related to TLV

Statistical Evaluation of Congestive Heart Failure on All-Cause Mortality

	p-values		
Term	Studies 0015, 0019	Study 0015	Study 0019
CHF	< 0.0001	< 0.0001	0.0096
TRT	0.922	0.426	0.5478
Interaction	**0.202**	**0.222**	**0.7031**

p-value by Wald test
CHF = congestive heart failure; TRT = treatment

Country Groupings by Study

Study 0015					
Group 1	Australia	Belgium	Canada	France	Israel
	Italy	United Kingdom	United States		
Group 2	Argentina	Brazil	Chile	South Africa	Taiwan
Group 3	Croatia	Czech Republic	Greece	India	Malaysia
	Malta	Peru	Poland	Turkey	
Study 0019					
Group 1	Australia	France	Canada	Israel	Spain
	United States				
Group 2	Argentina	Brazil	Chile	South Africa	
Group 3	Bulgaria	China	Croatia	Czech Republic	Estonia
	Georgia	Greece	Korea	Lebanon	Lithuania
	Mexico	Philippines	Poland	Romania	Russia
	Serbia/ Montenegro	Slovakia	Thailand	Ukraine	

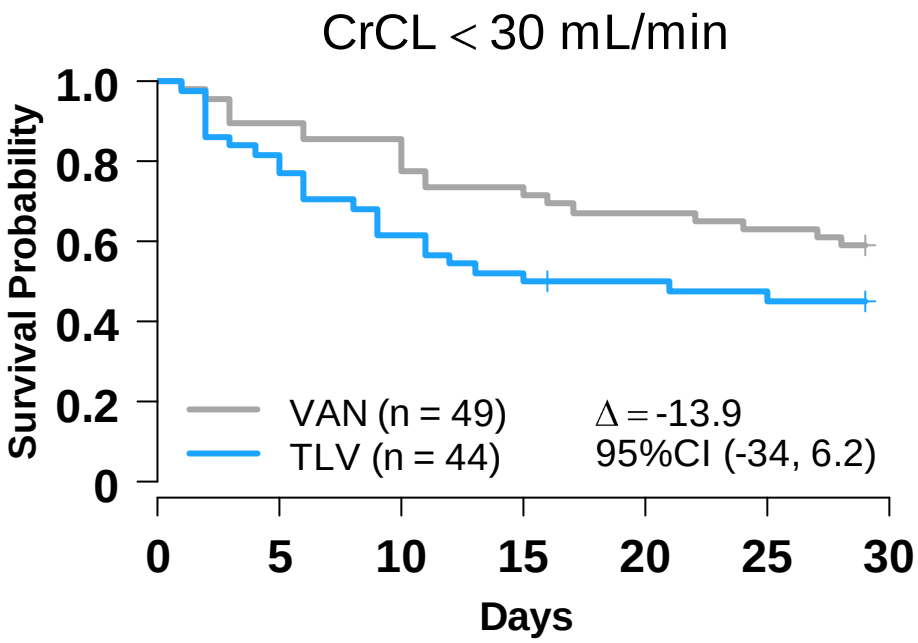
Country Enrollment by Study

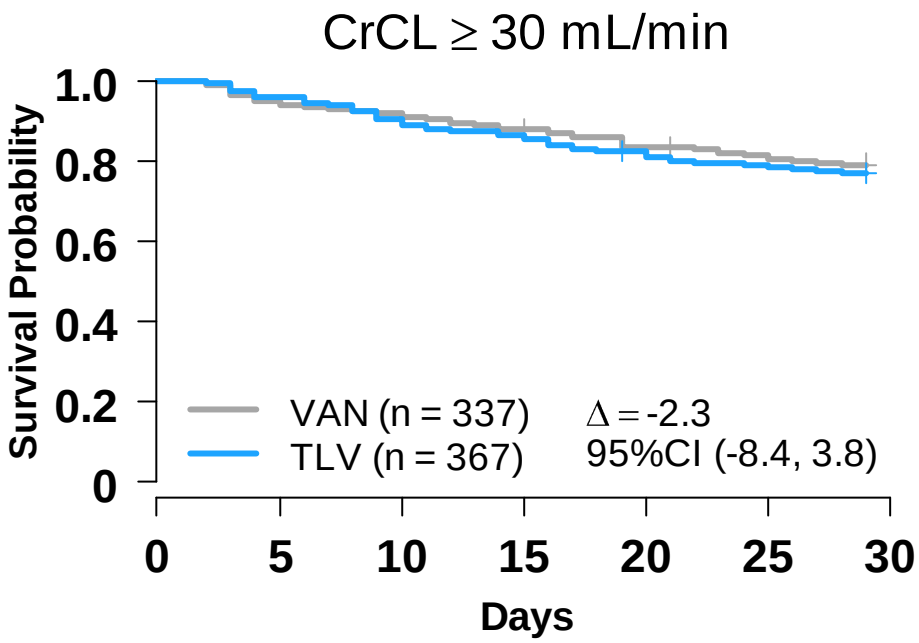
0015 Only		0019 Only		0015 and 0019		
Country	No. enrolled	Country	No. enrolled	Country	0015 enrolled	0019 enrolled
Belgium	8	Bulgaria	40	Argentina	48	39
India	85	China	64	Australia	45	23
Italy	7	Estonia	1	Brazil	26	33
Malaysia	20	Georgia	30	Canada	24	13
Malta	3	Lebanon	9	Chile	14	5
Peru	5	Lithuania	17	Croatia	59	4
Taiwan	63	Mexico	60	Czech Republic	1	4
Turkey	3	Philippines	17	France	32	2
UK	6	Romania	7	Greece	12	2
		Russia	50	Israel	49	76
		Serbia	17	Poland	2	10
		Slovakia	12	South Africa	4	10
		South Korea	53	United States	230	106
		Spain	2			
		Thailand	33			
		Ukraine	18			

Predictors of Mortality

- Independent risk factors for **mortality at day 28** were treatment in geographic region, baseline vasopressors, APACHE II score, age, cardiovascular disease, baseline bacteremia, multilobe pneumonia, MRSA infection at baseline, and acute renal failure (CrCL < 30 ml/min).

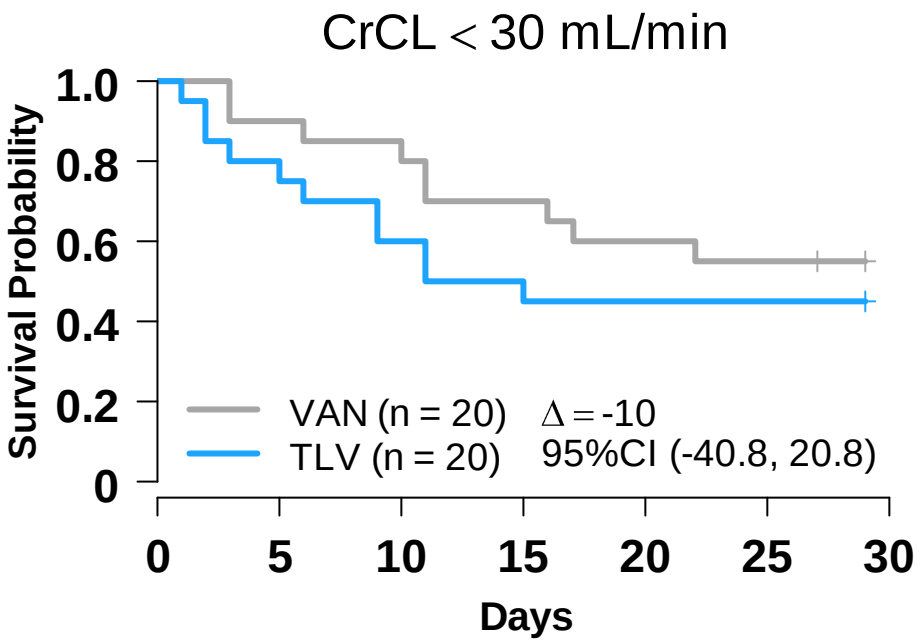
KM Survival Curves by Baseline CrCL
PP Population (Studies 0015, 0019)

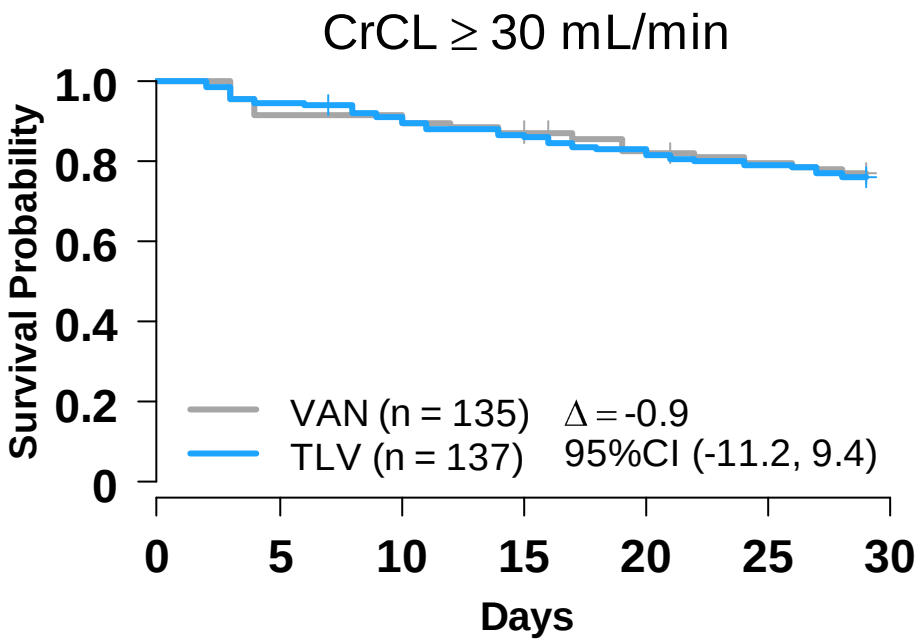




PP = Per Protocol = Patients with at least one Gram(+) organism at Study Entry.

KM Survival Curves by Baseline CrCL
ATS/IDSA–PP Population (Study 0015)





PP = Per-Protocol = Patients with at least 1 Gram(+) organism at Study Entry.

Cause of Death in Patients with Baseline CrCL 30-50 mL/min

Safety Population (Studies 0015, 0019)

	Patients, n (%)	
	TLV N = 143	VAN N = 150
NP	9 (6)	4 (3)
Respiratory related (non-NP)	6 (4)	5 (3)
Fungus / non-respiratory infection	2 (<1)	2 (<1)
Sepsis / shock	4 (3)	10 (7)
Multi organ failure	3 (2)	2 (<1)
Renal-related	1 (<1)	1 (<1)
Cardiac / cerebrovascular	10 (7)	9 (6)
Unknown cause	6 (4)	1 (<1)
Gastrointestinal	1 (<1)	1 (<1)
Other	2 (<1)	0
Total	44 (31)	35 (23)